

Peter C. Rimensberger
Editor

Pediatric and Neonatal Mechanical Ventilation

From Basics to
Clinical Practice

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Contents

Part I Basics of Respiratory Physiology and Mechanics in the Neonate and the Growing Child

1 Development of the Respiratory System (Including the Preterm Infant)	3
2 The Neonatal Neuromechanical Unit: Generalities of Operation	27
3 Basics of Gas Exchange	43
4 The Respiratory System	55

Part II Basics of Respiratory Support and Mechanical Ventilation

5 Neonatal Intubation (Specific Considerations)	115
6 Oxygen Supplementation, Delivery, and Physiologic Effects	123
7 Nasal CPAP: An Evidence-Based Assessment	135
8 Mechanical Ventilation	149
9 Airway Humidification	275
10 Specific Equipment Required for Home Mechanical Ventilation in Children	283

Part III Respiratory Mechanics in the Mechanically Ventilated Patient

11 Respiratory Mechanics in the Mechanically Ventilated Patient	293
--	------------

Part IV Respiratory Monitoring in the Mechanically Ventilated Patient

12	Classical Respiratory Monitoring	375
13	Monitoring of the Mechanical Behaviour of the Respiratory System During Controlled Mechanical Ventilation	421
14	Monitoring Lung Volumes During Mechanical Ventilation	441
15	Monitoring Interactions Between Spontaneous Respiration and Mechanical Inflations	473
16	Basic and Practically Useful Respiratory Monitoring of a Mechanically Ventilated Patient in Resource-Limited Countries	491

Part V Indications for Respiratory Support

17	Indications for Noninvasive Respiratory Support	503
18	Indications for Invasive Conventional Mechanical Ventilation	535
19	Indications for Nonconventional Ventilation Modes	559
20	Respiratory Support in Developing Countries Where Resources Are Limited	603

Part VI Clinical Use of Conventional Modes of Ventilator Support

21	Respirator Cycle Control Modes	615
-----------	---	------------

Part VII Clinical Use of Nonconventional Modes of Ventilator Support

22	Clinical Use of Nonconventional Modes of Ventilator Support	645
-----------	--	------------

Part VIII General Management of the Ventilator-Supported Patient

23	The Prone Position in Acute Lung Injury	671
-----------	--	------------

24	Respiratory Physiotherapy and Endotracheal Suctioning During Mechanical Ventilation	687
25	Fluid Management in the Ventilated Patient	711
 Part IX Permissive Hypercapnia		
26	Permissive Hypercapnia	727
27	Permissive Hypercapnia in Neonates: Specific Experience and Limitations	743
 Part X Adjunctive Therapies in Mechanically Ventilated Children and Neonates		
28	Surfactant	761
29	Selective Pulmonary Vasodilators	809
30	Drug Nebulization During Mechanical Ventilation	837
31	Use of Potent Inhalational Anesthetic Agents During Mechanical Ventilation	863
32	Rational Use of Adjunctive Therapies: Efficacy and Efficiency	887
 Part XI Complications of Mechanical Ventilation		
33	Ventilator-Associated Lung Injury	917
34	Gross Air Leaks	947
35	Infectious Complications in Mechanically Ventilated Patients	961
36	Post-extubation Stridor	981
 Part XII Bronchoscopy in Pediatric and Neonatal Intensive Care		
37	Bronchoscopy in Pediatric and Neonatal Intensive Care	1001

Part XIII Sedation, Analgesia and Neuromuscular Blockade During Mechanical Ventilation

- 38 Sedation, Analgesia and Neuromuscular Blockade in the Neonatal ICU 1019**
- 39 Sedation, Analgesia and Neuromuscular Blockade in the Paediatric ICU 1031**

Part XIV A Practical Approach to Noninvasive Mechanical Ventilation

- 40 Noninvasive Respiratory Support in the Neonate 1063**
- 41 Noninvasive Respiratory Support in the Paediatric Patient 1073**

Part XV Practical Evidence-Based and Goal-Directed Approach to Conventional Mechanical Ventilation

- 42 Setting the Ventilator in the NICU 1101**
- 43 Setting the Ventilator in the PICU 1127**
- 44 Approaches to Adverse Patient-Ventilator Interactions 1143**

Part XVI Practical Goal-Directed Approach to Nonconventional Mechanical Ventilation

- 45 High-Frequency Oscillatory Ventilation in the Neonate 1161**
- 46 High-Frequency Jet Ventilation (HFJV) 1173**

Part XVII Mechanical Ventilation in Various Pulmonary Pathologies

- 47 Acute Neonatal Respiratory Failure 1185**
- 48 Chronic Respiratory Failure in Neonates 1267**
- 49 Pediatric Acute Lung Injury 1279**
- 50 Bronchiolitis 1291**
- 51 Pediatric Asthma 1313**
- 52 Diaphragmatic Palsy 1325**

Part XVIII	Cardiopulmonary Interactions in the Mechanically Ventilated Patient	
53	Cardiopulmonary Interactions in the Ventilated Patient . . .	1333
Part XIX	Mechanical Ventilation in Infection, Sepsis and Organ Failure	
54	Mechanical Ventilation in Infection, Sepsis and Organ Failure	1369
Part XX	Mechanical Ventilation in Neuromuscular Disorders	
55	Mechanical Ventilation in Neuromuscular Disorders	1387
Part XXI	Specific Conditions	
56	Tracheostomy	1399
Part XXII	Weaning from Mechanical Ventilator Support	
57	Weaning Children from Mechanical Ventilator Support . . .	1415
58	Weaning from Mechanical Ventilator Support in Neonates	1425
Part XXIII	Automation of Mechanical Ventilation	
59	Explicit Computerized Protocols for Mechanical Ventilation in Children and Neonates	1435
60	Automated Control of Oxygen in Neonates	1447
61	Automation of Weaning in Children	1455
62	Automation of ALI/ARDS Ventilation in Children	1467
Part XXIV	Long-Term Outcomes After Mechanical Ventilation	
63	Long-Term Outcomes After Mechanical Ventilation in Neonates	1475
64	Long-Term Outcomes After Mechanical Ventilation in Children	1489

Part XXV Mechanical Ventilation in the Operating Room

65 Mechanical Ventilation in the Operating Room	1503
--	-------------

**Part XXVI Extracorporeal Membrane Oxygenation
in Acute Hypoxemic Respiratory Failure**

66 Extracorporeal Membrane Oxygenation in Acute Hypoxic Respiratory Failure	1525
--	-------------

**Part XXVII Evaluating Mechanical Ventilators for Use
in Neonatal and Pediatric Patients**

67 Evaluating Mechanical Ventilators for Use in Neonatal and Pediatric Patients	1537
--	-------------

**Part XXVIII Organization and Management of Mechanical
Ventilation Worldwide**

68 Organization Characteristics in North Africa	1565
--	-------------

69 Organization Characteristics in North America.	1571
--	-------------

70 Organization Characteristics in South America.	1575
--	-------------

71 Organization Characteristics in Europe	1583
--	-------------

72 Organization Characteristics in Oceania.	1589
--	-------------

Part XXIX Ethical Concerns

73 Ethical Concerns	1599
--------------------------------------	-------------

Index	1613
------------------------	-------------

Part I

Basics of Respiratory Physiology and Mechanics in the Neonate and the Growing Child

Development of the Respiratory System (Including the Preterm Infant)

1

Stephen Joza and Martin Post

Abbreviations

ARDS	Acute respiratory distress syndrome
BASCs	Bronchoalveolar stem cells
BPD	Bronchopulmonary dysplasia
CDH	Congenital diaphragmatic hernia
DL _{CO}	Pulmonary diffusing capacity for carbon monoxide
E	Embryonic day
ECM	Extracellular matrix
FGF	Fibroblast growth factor
Flk-1	Fetal liver kinase-1
Flt-1	Fms-like tyrosine kinase
Fox	Forkhead box
GC	Glucocorticoid

Hif	Hypoxia-inducible factor
Hox	Homeobox
IPF	Idiopathic pulmonary fibrosis
MMP	Matrix metalloproteinase
NF-κB	Nuclear factor κB
PDA	Patent ductus arteriosus
PDGF	Platelet-derived growth factor
pnd	Postnatal day
RA	Retinoic acid
RDS	Respiratory distress syndrome
SHH	Sonic hedgehog
SP-C	Surfactant protein C
TGF-β	Transforming growth factor beta
TIMP	Tissue inhibitor of metalloproteinases
TTF-1	Thyroid transcription factor 1
V _A	Alveolar volume
VEGF-A	Vascular endothelial growth factor A
VEGFR	Vascular endothelial growth factor receptor

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1.1 Prenatal Development

1.1.1 Embryonic and Fetal Development of the Airways

Fetal lung development is primarily concerned with the establishment of the conducting airway system and associated vasculature and is classically divided into five descriptive stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar (Fig. 1.1, Table 1.1) (Burri 1984). In the standard model of lung morphogenesis, human airway development begins in the embryonic 4th

week by the appearance of a ventrolateral diverticulum from the foregut endoderm invading into the surrounding splanchnopleuric mesoderm. This implies a common origin of the trachea and esophagus, although this view has recently been challenged by the proposal that the two arise from distinct germ cell regions of the endoderm which are brought together and later septated as a result of embryonic head folding (Brown and James 2009). This may explain, for example, the opposing directions of the mucociliary escalator in the tracheobronchial tree (which shifts mucous cranially) from the mucociliary cascade of the upper airway (which shifts mucous into the esophagus and ultimately into the stomach). In either case, the epithelium of the conducting airways and lung parenchyma will develop from this region of specified endoderm, while the various structural components of the lungs, including elastic tissue, smooth muscle surrounding the contractile airways and vessels, cartilage of the trachea and bronchi, the vascular and lymphatic systems, and connective interstitial tissue, all derive from the surrounding mesoderm (Burri 1984).

Expression of the definitive distal lung epithelial marker, surfactant protein C (SP-C), is detectable as early as E9.5 in the prospective murine endoderm (Serls et al. 2005). Lung specification and positioning in the foregut relies upon instructive and concentration-dependent signalling by the secreted fibroblast growth factor (FGF) family from the adjacent cardiac mesoderm as well as reciprocal sonic hedgehog (SHH)-GLI signalling between the foregut endoderm and splanchnopleuric mesoderm (Motoyama et al. 1998; Serls et al. 2005). Such tissue interactions at this early stage presage the critical importance that epithelial-mesenchymal signalling will play in the growth and maintenance of the airway epithelium and pulmonary vasculature throughout all stages of lung development.

Right-left asymmetry is already established by 4.5 weeks since the lung anlage is divided into three right-sided and two left-sided diverticula (four right-sided and one left-sided in mice), which corresponds to the adult configuration of the lobar bronchi and lung lobes. Various factors

known to be involved in global axis specification have been implicated in this early patterning, including several members of the transforming growth factor (TGF)- β family (Lefty-1 and Lefty-2, Nodal) and Pitx-2, since in all cases, gene deletion in mice causes pulmonary isomerism (Tsukui et al. 1999). Retinoic acid (RA) and SHH appear to be master regulators of restricting appropriate expression of these growth factors (Lin et al. 1999; Meno et al. 1998).

1.1.2 Branching Morphogenesis

The pseudoglandular phase (weeks 5–17 in humans) establishes all the prospective pre-acinar airways (i.e., those proximal to the respiratory bronchioles). This is achieved by branching morphogenesis, in which epithelial buds at the periphery follow a pattern of repetitive dichotomous branching, mediated by reciprocal interactions between the outgrowing epithelium and the surrounding mesenchyme. The importance of such interactions has been demonstrated in classic transplantation experiments using cultured explants, in which the pulmonary epithelium degenerates if isolated from the surrounding mesenchyme, and vice versa (Masters 1976). Conversely, recombination of mesenchyme taken from areas of active branching with non-branching tracheal epithelium induced lung-like epithelial branching, demonstrating both the plasticity of the primordial lung epithelium and the specificity of mesenchymal inductive signalling (Shannon et al. 1998).

Recent analysis in mice has suggested that the orderly development of the millions of branches in the mammalian lung follows a remarkably simple set of only three genetically encoded “subroutines” (Metzger et al. 2008). The first, termed domain branching, sprouts daughter branches at specific sites along and around the circumference of the parent branch. The next two subroutines, planar and orthogonal bifurcation, are responsible for establishing additional tertiary and later generation branches which extend from those developed by domain branching. This occurs from repeated bifurcations of the branch

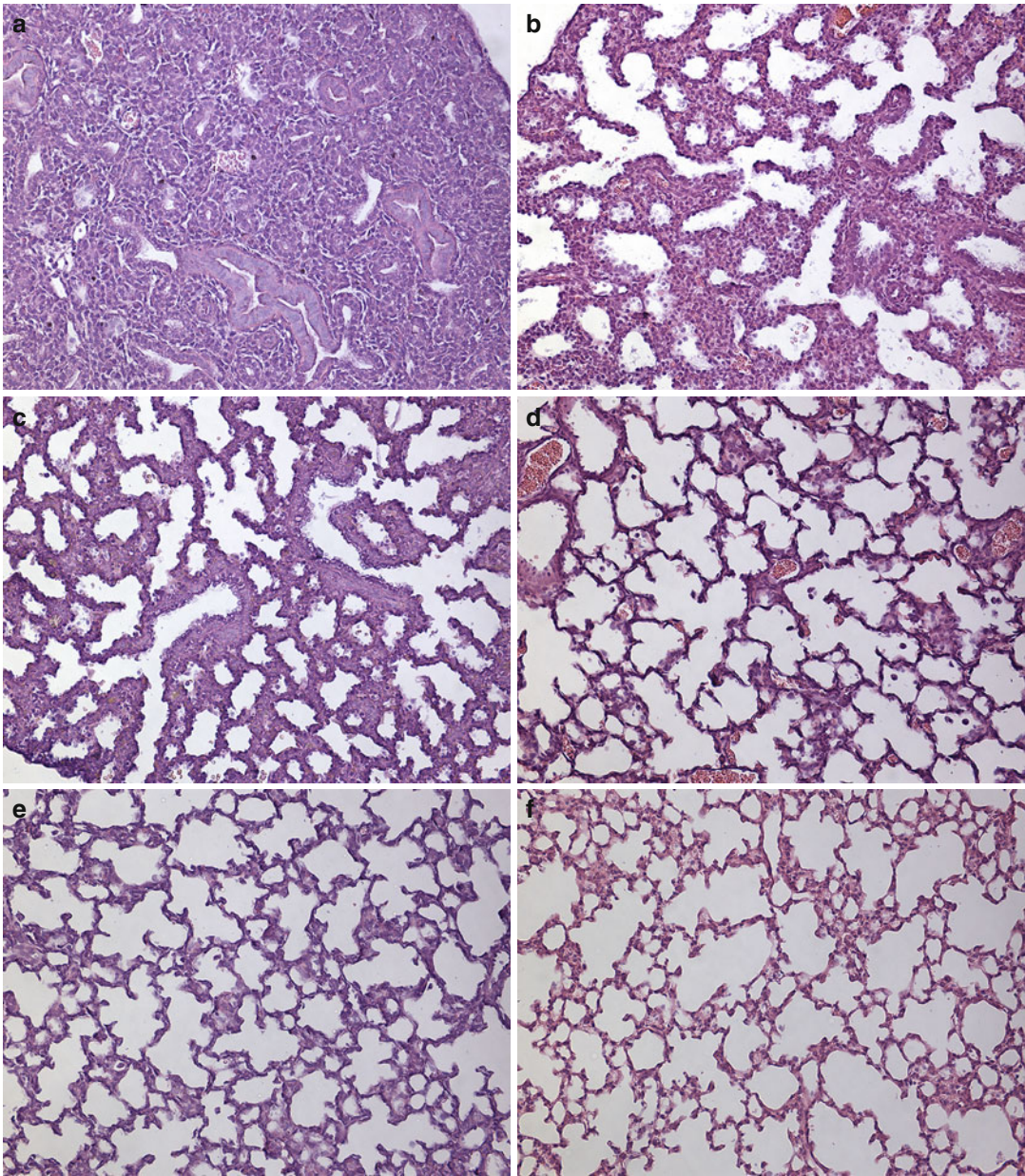


Fig. 1.1 The stages of lung development. H&E staining of mouse lungs are shown during the pseudoglandular (**a**, E13.5), canalicular (**b**, E15.5), saccular (**c**, E18.5), and

alveolar stages (**d–f**, postnatal days 2, 8, 21). Progressive expansion of the airways and interstitial thinning are observed (Magnification, 200×)

tips along the anterior-posterior axis (planar) or in clusters rotated at 90° (orthogonal). These three subroutines, when stereotyped in just three possible combinations, essentially form all the branching events observed during early pulmonary development. Importantly, these subroutines

appear to be under the control of a master routine, which outlines a general developmental plan each branching lineage will follow. In contrast, localized signalling molecules are involved in the direction of the morphogenetic events themselves (mesenchymal invasion, epithelial budding, etc.).

Table 1.1 The timing and events of pre- and postnatal lung development

Stage	Developmental age			Key morphogenetic events
	Human	Mouse	Rat	
Embryonic	4–7 weeks	E9.5–E12	E11–E13	Specification and differentiation from the primitive endoderm Formation of the lobar bronchi and left/right asymmetry
Pseudoglandular	5–17 weeks	E12–E16.5	E13–E18.5	Establishment of the prospective conducting (pre-acinar) airways via branching morphogenesis Appearance of the presumptive acini—the respiratory units of the lung Differentiation of the airway epithelium begins
Canalicular	16–26 weeks	E16.5–E17.5	E18.5–E20	Establishment of the parenchyma by enhanced capillarization, pneumocyte differentiation, and reduction in mesenchyme Surfactant synthesis begins (~22–24 weeks in humans)
Saccular	24 weeks–term	E17.5–pnd 4	E21–pnd 4	Further development and expansion of the airspaces
Alveolar	36 weeks–min. 2 years postnatal	pnd 4–pnd 36	pnd 4–pnd 60	Secondary septation dramatically enhances the parenchymal surface area Mesenchymal thinning Microvascular maturation

Rodent models are included and roughly comparable to humans despite morphological differences in the airway tree and cell content and distribution (Mercer et al. 1994, #855)

These regulators have been the subject of much focus and have been reviewed in detail elsewhere (Cardoso and Lu 2006; Massaro et al. 2004).

1.1.3 Differentiation of the Conducting Airway Epithelium

As one travels along the proximodistal axis of the 2^{23} branches of the mature airways, marked changes in epithelial cell type and distribution are observed, underscoring the variety of regional differences in epithelial function. The pseudostratified and columnar epithelium of the larger airways (branches 2^0 – 2^5) is chiefly composed of basal, ciliated epithelium, goblet cells, and indeterminate cells, all of which rest upon the basal membrane and which overlie layers of smooth muscle cells (Mercer et al. 1994). In addition, submucosal glands are contiguous with the epithelium from the larynx to the small bronchi

(Jeffery and Li 1997). Upon reaching the smaller airways (branches 2^6 – 2^{23}), the epithelial lining decreases in height, becoming principally composed of ciliated cuboidal epithelium and Clara secretory cells. Notably, submucosal glands are absent and goblet cells are normally rare at this level, explaining the absence of mucus secretion (Lumsden et al. 1984).

The diversity and organization of the mature airway epithelium develops as a result of the coordinated differentiation and maturation of the primitive fetal endoderm, beginning in the mid-pseudoglandular stage. Prior to differentiation, the primordial airways are composed of a thick pseudostratified epithelial lining with little to no lumen, resembling the esophagus (Adamson 1997). Such primitive fetal cells have a high nuclear-to-cytoplasmic ratio, indicative of their undifferentiated state, and glycogen, which will fuel later differentiation (Burri 1997). Over the course of airway branching and maturation, this primitive epithelium is dramatically remodelled along the proximodistal

axis, beginning in the larger airways and spreading distally, ultimately resulting in airway expansion and decreasing epithelial thickness at all levels of the airways (Adamson 1997). Indeed, airway diameter increases linearly with age in the fetus and neonate, regardless of prematurity (Hislop and Haworth 1989).

Differentiation of both the epithelium and mesenchyme is apparent by the mid-pseudoglandular stage: ciliated epithelium is observed in the tracheobronchial epithelium by the 10th week and in the most peripheral airways by the 13th, while cartilage and smooth muscle cell precursors are found in the trachea by the 10th week, extending towards the segmental bronchi by the 12th week (Bucher and Reid 1961; Burri 1984). During gestation, lung fluid is secreted by the epithelium into the lumen of the future airways. Spontaneous peristaltic contractions of smooth muscle throughout gestation until birth are essential for driving lung fluid distally towards the compliant terminal buds, which may promote airway differentiation and branching via mechanotransduction (Schittny et al. 2000). Submucosal glands are observable by the 14th week, while mucus-containing goblet cells are identifiable by the 13th week in the trachea and large bronchi, extending to the most proximal intrasegmental bronchi by the 24th week (Bucher and Reid 1961). Interestingly, the frequency of goblet cells peaks during mid-gestation, comprising up to 35 % of the bronchial epithelium, before steadily reducing in number to ~12 % in adults (Jeffery 1998; Mercer et al. 1994). Basal cells in the large airways and Clara cells in the bronchioles have been described as early as 10 and 16 weeks gestation, respectively, although the timing of their maturation is speculative and may only fully mature by the mid-canalicular stage (Bucher and Reid 1961; Jeffery 1998; Jeffery et al. 1992).

1.1.4 The Establishment of the Air-Blood Interface

Following branching morphogenesis, the terminal bud epithelium is reduced from a pseudostratified

form to simple cuboidal, marking the appearance of the future acini. During the canalicular stage (weeks 16–26), Type II cell differentiation begins, indicated morphologically by the dramatic reduction of intracellular glycogen content, in part from bolstering surfactant synthesis, and the appearance of intracellular lamellar bodies, the storage form of pulmonary surfactant (Adamson 1997). After undergoing structural transformations, such lamellar bodies are secreted into the developing air sacs, where they will form pulmonary surfactant. Importantly, surfactant secretion is present by ~22–24 weeks in the human, and by 80–85 % gestation in most other species, although due to uneven distribution, it appears to be more abundant in apical than basal regions (Burri 1997). Hence, surfactant therapy has been instrumental in the treatment of respiratory distress syndrome (RDS) in premature infants.

The air-blood interface begins to develop as the airspaces widen at the expense of mesenchymal volume and cell number, which is resultant from both mesenchymal apoptosis and a sharp reduction in fibroblast proliferation (Adamson 1997; Stiles et al. 2001). Indeed, during the canalicular stage, the epithelial population doubles in number, reflecting the continuous epithelial cell proliferation and expansion of the airways into the mesenchyme (Adamson 1997). Meanwhile, the developing capillaries begin to “canalize” the lung parenchymal interstitium, forming in close apposition to the epithelium. Concurrently, squamous Type I pneumocytes begin to differentiate from the cuboidal epithelium overlying the invading capillary layers, resulting in a shared basement membrane with the capillary endothelium and thus the formation of the ultrathin air-blood interface alveolar parenchyma. A sharp decline in proliferating epithelium during the canalicular to saccular transition reflects the differentiation of the epithelium into pneumocytes (Adamson 1997). By the end of the saccular phase (26th week–term), the terminal airways exist as primitive saccules which, during the alveolar phase, will develop into functional alveolar units.

Much focus has centered upon the mechanism of Type I cell differentiation, since despite comprising only 8 % of total cells in the adult lung,

Type I cells cover over 95 % of the parenchymal surface and are thus at the forefront to the pathogenesis of various major lung diseases (Crystal et al. 2008). Moreover, airway epithelial turnover in the adult is estimated to occur every 30–50 days, although the mechanism of this repopulation is not understood (Crystal et al. 2008). Autoradiographic studies in the rat lung have long suggested that Type I cells differentiate from Type II cells during normal fetal and postnatal development (Kauffman et al. 1974) and after rapid Type II proliferation and replacement of the lung parenchyma following acute lung injury (Evans et al. 1975). However, the stem or progenitor cells which act as the source of new epithelial cells have not been conclusively determined (Crystal et al. 2008). A very recent study using a post-pneumonectomy model of stimulating compensatory lung regrowth has suggested that distinct cells at the bronchoalveolar junction (bronchoalveolar stem cells, BASCs) act as stem cells for a subpopulation of transit-amplifying Type II cells, which in turn differentiate into Type I cells (Nolen-Walston et al. 2008). However, significant cell migration of such BASCs to the sites of airway damage would likely be required, while, based upon the study's own theoretical estimates, the contribution of BASCs towards alveolar epithelial regeneration may well be minimal.

1.1.5 Development of the Embryonic and Fetal Pulmonary Vascular System

The anatomic origin of the pulmonary circulation is the right ventricle. Throughout gestation, the pulmonary flow is estimated to be only 11 % of the combined biventricular output, but following the closure of the foramen ovale and ductus arteriosus at birth, it receives 100 % of the cardiac output (Mielke and Benda 2001). Patent ductus arteriosus (PDA) in the neonate is associated with deterioration of pulmonary function and alveolar development (i.e., BPD), in part due to pulmonary edema from left-to-right shunt (Massaro et al. 2004). Intriguingly, while pharmacological

closure of PDA prevents the incidence of such defects, prophylactic surgical ligation of the ductus arteriosus actually increased the risk of developing BPD, although the mechanism remains unclear (Clyman et al. 2009).

1.1.5.1 The Extrapulmonary Vessels

In the development of the pulmonary vasculature, both the pulmonary trunk and pulmonary arch arteries receive contributions from cardiac neural crest cells, which migrate from the dorsal neural tube and populate the pharyngeal arches and outflow tract of the developing heart (Kirby and Waldo 1995). Between the 4th and 8th weeks of gestation, concurrent with the start of lung budding, the cardiac outflow tract is septated into the aorta and pulmonary trunk from either the fusion of the distal and proximal outflow cushions of the embryonic heart, the elongation of an aortopulmonary septum, or a combination of both paradigms (Webb et al. 2003). During this process, the aortopulmonary septum can be observed growing in between the fourth and sixth paired pharyngeal arches, which will form components of the mature vasculature: the fourth pharyngeal arches contribute to the aortic arch and subclavian arteries, while the right sixth regresses and the left sixth persists to form the ductus arteriosus and the pulmonary arteries by the 7th week (Poelmann and Gittenberger-de Groot 2005).

1.1.5.2 The Intrapulmonary Vessels and Microcirculation

The development of the intrapulmonary vessels (i.e., the branching arterial tree most closely associated with the airways and the pulmonary veins running along the periphery of the terminal respiratory units) and the peripheral microvasculature of the lung parenchyma has sparked much recent investigation (de Mello and Reid 2000; de Mello et al. 1997; Hall et al. 2000, 2002; Maeda et al. 2002; Parera et al. 2005; Schachtner et al. 2000; Schwarz et al. 2009). Although several hypotheses have been put forward, two essential processes are implicated: vasculogenesis, which describes the de novo formation of primitive blood plexuses from the aggregation of mesodermal endothelial progenitor cells (angioblasts),

and angiogenesis, wherein new vessels are formed by sprouting from existing ones (Poole and Coffin 1989). Intuitively, one might predict that the two processes follow a successive program. For example, in the establishment of the embryonic vascular network, a primitive vascular plexus formed by vasculogenesis is subsequently remodelled and expanded by angiogenesis (Patan 2000). In the development of the pulmonary vasculature, however, the degree of involvement of either process has not been definitively answered, reflecting differences in methodology and interpretation, and possibly the intrinsic morphological differences among and between human samples and animals models.

The earliest comprehensive studies in the mouse and human described the proximal macrovasculature deriving from angiogenic sprouting of the pulmonary vascular trunks, while the distal microvasculature formed by vasculogenesis of hematopoietic cell lakes diffusely coalescing around actively branching distal airway epithelium, starting in the late embryonic phase (de Mello and Reid 2000; de Mello et al. 1997). In this model, the two processes function concurrently but independently, with fusion of the proximal vasculature and peripheral capillary networks occurring relatively late in pulmonary vascular development (E13–14 in the mouse and 10–11 weeks in the human). In contrast, others described the patency between the proximal and distal vessels—and hence a functional pulmonary circulation—occurring much earlier in development (by E10.5 in mice and 34 days gestation in humans, concurrent with the formation of the first airway branches and tracheal separation from the esophagus) (Hall et al. 2000, 2002; Schachtner et al. 2000). This implicated vasculogenesis as the predominate mechanism of the intrapulmonary vascular system, in which endothelial cell precursors (angioblasts) form primary capillary plexuses surrounding developing epithelial buds in the lung periphery. These plexuses continue to expand and coalesce to form arteries and veins more proximal to the terminal buds, suggesting that unlike the development of the airways, which branch and develop centrifugally from the hilum towards the periphery, the primordial

vascular system starts from the periphery and expands proximally (Hall et al. 2000, 2002). However, recent reports have suggested that early pulmonary vascular growth and expansion occurs primarily by angiogenesis (Parera et al. 2005; Schwarz et al. 2009). In agreement with previous studies (Hall et al. 2000; Schachtner et al. 2000), vascular circulation connected to the central vessels appears to be in place at the earliest signs of lung development by the observation of primitive erythrocytes in the lumen of plexiform vessels surrounding growing epithelial buds (at E9.5 in mice) (Parera et al. 2005). However, angiogenesis was suggested to occur predominantly because of the description of these newly formed plexuses remodelling into proximal vessels and the absence of putative angioblasts as assessed by immunostaining for vascular endothelial growth factor receptor (VEGFR)-2 and CD34 (early endothelial markers). Hence, rather than distal vasculogenesis, they proposed distal angiogenesis, in which new capillaries arise from existing ones at the lung periphery (Fig. 1.2). Schwarz and coauthors (2009) agree that the expansion of the pulmonary vasculature in mice occurs primarily by angiogenesis, based upon the co-expression of CD31, phosphorylated VEGFR-2, and fluorescent lectin perfusion, which combined indicated the presence of functional vessels by E11.5. They suggest that previous studies which used VEGFR-2 (rather than phosphorylated VEGFR-2) to indicate angioblasts (and hence vasculogenesis) (Schachtner et al. 2000) reflect uncommitted pluripotent cells. Furthermore, they put forth the interesting model that vessel ingrowth begins within the lung mesenchyme and not in close apposition to the epithelial-mesenchymal interface as is commonly described (e.g., Parera et al. (2005)). In this model, new vessels must then expand and extend from the mesenchyme towards the epithelial-mesenchymal junction via angiogenesis beginning at E14.5, likely as a response to vascular endothelial growth factor (VEGF-A) signalling originating from the basilar epithelium. This would suggest that before E14.5, vessels may not necessarily follow or influence airway branching, although diffusible tissue interactions between the vasculature and

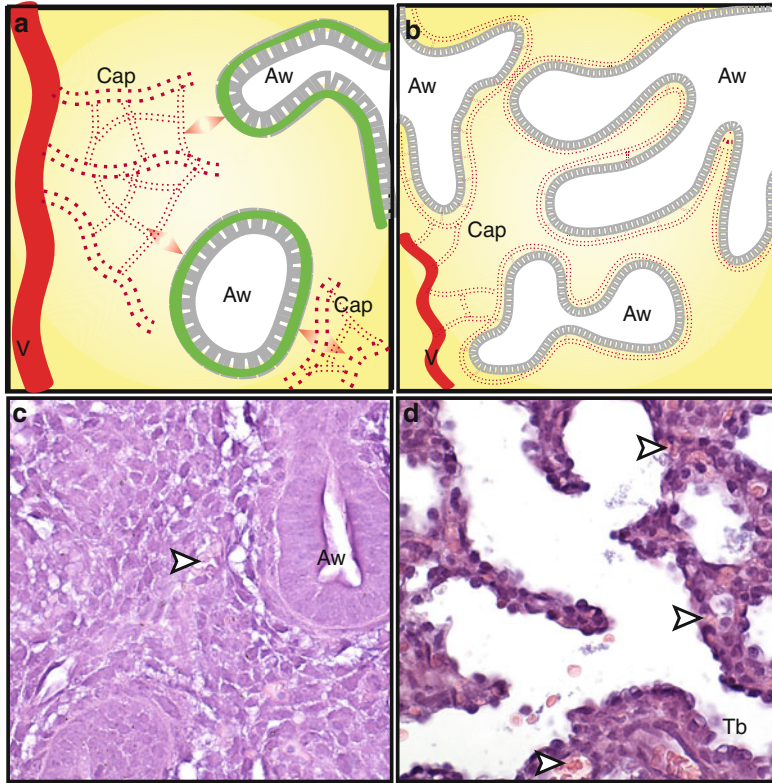


Fig. 1.2 Early vessel formation has been proposed to occur by angiogenic sprouting from preexisting vessels concurrent with the start of lung development. Sprouting occurs within the lung mesenchyme, but not in regions of the epithelial-mesenchymal border early in development (a), although diffusible interactions between the endothelium and epithelium are necessary for continued growth and maintenance (double arrowheads). During the pseudoglandular and canalicular stages, the vasculature

expands towards the epithelial-mesenchymal junction, possibly as a response to VEGF-A secretion from the basilar epithelium, forming the air-blood interface (b). H&E staining of mouse lung shows erythrocytes (arrowheads) within the mesenchyme at E13.5 (c) and in close contact with the epithelium at E17.5 (d). Aw developing airway, Cap capillary, Tb terminal bronchiole, V preexisting vessel (Magnification in c and d, 400×)

epithelium are still required for normal growth and maintenance of both, which is consistent with the degeneration of either tissue layer when cultured in isolation (Gebb and Shannon 2000; Shannon et al. 1998, 1999). Indeed, while chemical inhibition of VEGFR-2 signalling halted vascular growth in E11.5 mouse explants, epithelial branching was only modestly attenuated (Groenman et al. 2007). Hence, disruption of this vessel extension to the primordial parenchyma by inhibiting VEGF-A signalling would prevent the progression of epithelial-endothelial reciprocal signalling and thus the blockage of further lung morphogenesis beyond E14.5, as observed (van Tuyl et al. 2005; Yamamoto et al. 2007).

1.2 Postnatal Lung Development

1.2.1 Postnatal Lung Development: Alveolarization

Normal lung function requires the development of an air-blood barrier of maximal surface area and minimal thinness. This is achieved by the formation of the alveoli beginning in late prenatal human development (week 36) and continuing through early postnatal life in a process termed “alveolarization” (also referred to as “alveologensis”) (Fig. 1.3). Although birth is often considered the end of organogenesis and the start of

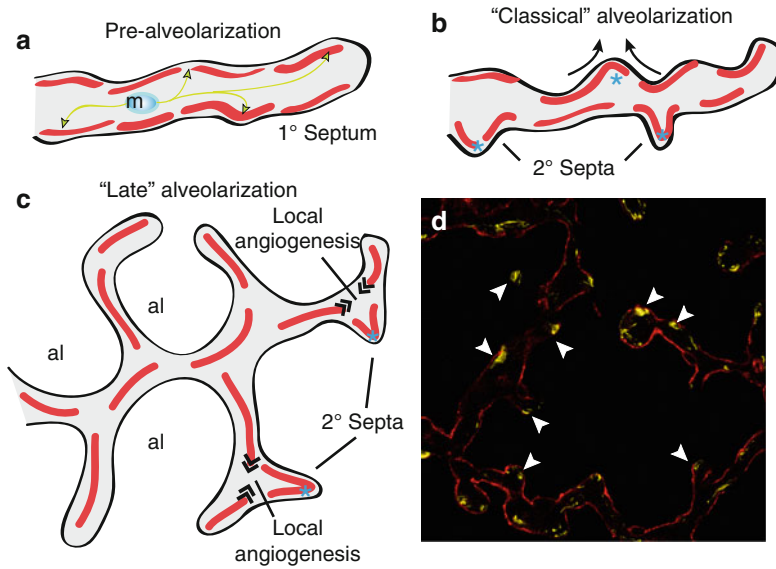


Fig. 1.3 Prior to alveolarization, the future lung alveoli exist as primitive sacculi containing a capillary bilayer (a). Myofibroblasts migrate towards distinct sites in the primary sacculi and deposit tropoelastin at the future sites of secondary septal formation, ultimately forming localized accumulations of elastin (*arrowheads*). During classical alveolarization (b), the primary sacculi are subdivided into alveoli by secondary septation, while the capillary bilayer is subsequently remodelled into a monolayer

during microvascular maturation. During late alveolarization (c), localized angiogenesis at the base of secondary septa is required to maintain the continuity of the capillary monolayer. Secondary septa are observed in an immunostaining with the myofibroblast marker, alpha smooth muscle actin (*arrowheads*), in a pnd 8 mouse lung doubly stained with the Type I cell marker T1 α , which outlines the epithelial surface (d), magnification 400 $\times$

growth and maturation, the development and maturation of alveoli in humans and most other mammals is largely, and often exclusively, a post-natal process, ceasing only several years after birth in humans (Burri 1997). The end result of alveolarization and isometric parenchymal growth produces a lung with alveolar and capillary surface areas at least 20 times that of the neonate (Zeltner et al. 1987).

1.2.2 The Formation of the Alveoli

Alveolarization occurs as the immature sacculi which form the lung parenchyma are subdivided into smaller units by the formation and subsequent extension of secondary septa (singular, “septum”). This is followed by a period of microvascular maturation, in which the double capillary layer lining the alveoli is remodelled into a monolayer by capillary fusion and

intussusceptive growth. The seminal reports which introduced this model of alveolarization proposed that the two processes acted somewhat independently of each other: secondary septation was proposed to occur mostly between postnatal days (pnd) 4–14 in the rat, followed successively by microvascular maturation primarily during the third postnatal week (Burri 1974). Hence, the formation of alveoli by further septation was thought impossible following the completion of microvascular maturation, which placed the endpoint of alveolarization in rats and humans conservatively at 3 weeks and 2–3 years postnatal, respectively (Zeltner et al. 1987).

The determination of the endpoint of alveolar development is of much clinical relevance since a longer period of alveolarization increases the window of opportunity for morphological disruptions to occur. For example, alveolar development could arrest without subsequent “catch-up”

as a consequence of acute lung disease experienced early in life or from iatrogenic interventions, such as from glucocorticoid therapy in the treatment of asthma. Again, while the postnatal gas-exchange surface area dramatically increases with respect to longitudinal growth (Zeltner et al. 1987), this could arise solely from the isometric growth of the lung parenchyma rather than from the formation of new alveolar septa.

In fact, two recent stereological studies in mice and rats from one group have reported that isometric growth of the lung can only account for a modest increase in septal surface area during postnatal development (Mund et al. 2008; Schittny et al. 2008). By their estimates, the formation of alveoli occurs well beyond the stage of microvascular maturation, ceasing only in young adulthood in mice (pnd 36) and rats (pnd 60). These authors propose that alveolarization proceeds in two phases: “classical” alveolarization occurs prior to microvascular maturation (pnd 4–21) by the formation of secondary septa from immature (capillary bilayer) septa, which accounts for 40 and 50 % of septa present in the adult rat and mouse, respectively, and a second “late” phase (pnd 21–adulthood), in which alveolar septa must arise from mature (capillary monolayer) septa, accounting for 50 and 40 % of septa in the adult rat and mouse, respectively (the remaining 10 % of septa appear to be formed prenatally from branching morphogenesis) (Mund et al. 2008; Schittny et al. 2008). Importantly, the second phase appears to require localized angiogenesis at the base of the newly forming septum, since the capillary microvasculature has already thinned to a monolayer (Mund et al. 2008; Schittny et al. 2008). These results are in agreement with a similar stereological study in rhesus monkeys, which also reported alveolarization continuing through to the 8th postnatal year (Hyde et al. 2007), suggesting that the same may well be true in humans.

While similar analyses in humans are for practical reasons not possible, measurements of pulmonary diffusing capacity for carbon monoxide (DL_{CO} , used indirectly as a measurement of parenchymal surface area) and alveolar volume (V_A) in infants aged 2–23 months showed that

the DL_{CO}/V_A ratio remained constant, suggesting that lung growth occurred primarily by alveolar septation within the first 2 years of life (Balinotti et al. 2009). In contrast, DL_{CO}/V_A decreased with increasing age in children ages 6–17 years, consistent with isometric parenchymal lung growth outpacing alveolar septation (Stam et al. 1996). However this does not definitively answer the question of when alveolar development in humans is completed. Indeed, the size of the terminal airspaces in mice and rats was observed to change over the course of postnatal development as a result of the changing rates of septal formation and parenchymal growth, which vary over maturation, although with some interspecies variability (Mund et al. 2008; Schittny et al. 2008). Hence, whether alveolarization in humans principally occurs en masse in a relatively short period of time (so-called bulk alveolarization), or more gradually, and perhaps variably, alongside longitudinal growth, has yet to be determined.

1.2.3 The Regulation of Secondary Septation

BPD is a condition which affects nearly one third of neonates with birth weights less than 1,000 g (Walsh et al. 2006). The aetiology of the disease is multifactorial and develops in response to lung injury experienced from both environmental factors (hyperoxia relative to in utero, infection, nutritional deficits, lung immaturity) and strategies designed to manage premature infant care (mechanical ventilation, antenatal steroid administration). Genetic susceptibility, such as with respect to surfactant synthesis and inflammatory response, is also being recognized as a significant contributing factor (Abman et al. 2008).

BPD is presently characterized by an arrest in alveolar septation and dysmorphic vascular growth, leading to a reduction in gas-exchange surface area and respiratory potential (Bourbon et al. 2005). Similarly, gas exchange is impaired in adult-onset emphysema, which arises from damage to preexisting alveoli (Morris and Sheppard 2006). Studies which identify the fundamental regulators

which orchestrate normal alveolarization and how these pathways are disrupted in conditions such as BPD and emphysema are critical for the development of therapies which can treat these debilitating diseases. However, the mechanisms involved in the various morphogenetic processes of alveolarization are not well understood. Multiple stimuli, including growth and transcription factors, extracellular matrix (ECM) proteins, hormones, and oxygen exposure coordinated through autocrine and paracrine interactions between the epithelium, fibroblast derivatives, and the ECM, work together in concert to sculpt the alveolar architecture (Roth-Kleiner and Post 2005). Conversely, dysregulation of these interactions results in arrested alveolar development. Next we provide a short updated review of factors known to be essential for normal alveolarization and which have largely been uncovered in the context of chronic lung diseases, such as BPD.

1.2.3.1 ECM

The ECM comprises the basal lamina and interstitium subjacent to the parenchyma, and its composition is critical for the mechanical properties of the lung as well as the regulation of cell growth, morphogenesis, and differentiation. Although the principal component of the ECM is collagen and adherent glycoproteins, elastic fibers interwoven into the structure at the septal interstitial tips and alveolar free edges contribute most to the structural integrity and compliance of the lung and stretch-induced signal transduction during each respiratory cycle (Mercer and Crapo 1990). Elastic fibers are formed when tropoelastin, secreted from myofibroblasts, coalesces and cross-links upon a microfibril scaffolding. The attachment of the scaffolding to the cell membrane is regulated by various matrix proteins, while cross-linking is induced by the action of lysyl oxidases, thus producing insoluble elastin fibers (Bland et al. 2008). The absolute quantity of parenchymal elastic tissue increases slowly during gestational weeks 22–30, but rapidly increases thereafter, correlating with its proposed function in secondary crest formation (Thibeault et al. 2000).

Prior to secondary crest eruption from the saccular walls, myofibroblasts proliferate and

migrate to discrete areas of the saccular walls, where they deposit tropoelastin at the sites of future secondary crest formation, thus forming the elastic fibers. It has been suggested that septal formation is initiated by mechanical stress applied to these elastic fibers which lift up the alveolar walls, although the mechanism is unclear (Burri 1997). Indeed, tenascin-C, known to be expressed in relation to increasing mechanical load, is present at the rising septal tips (Massaro et al. 2004). Destruction of elastin fibers contributes to the pathogenesis of emphysema, while elastin-null mice are perinatally lethal and exhibit marked reduction in tissue septa and distal air sacs, reminiscent of emphysema (Wendel et al. 2000). Furthermore, mice with only one elastin-encoding allele have increased susceptibility to smoke-induced emphysema (Shifren et al. 2007).

Interestingly, dysregulation of elastin deposition has been associated with alveolar malformation. Ovine and murine mechanical ventilation models of BPD as well as BPD infants display abnormally enhanced elastin deposition and distribution throughout the alveolar airspaces and secondary crests instead of focal concentrations at the septal tips (Bland et al. 2008; Pierce et al. 1997; Thibeault et al. 2000). In these models, lung expression of growth factors known to regulate lung septation, such as VEGF-A, platelet-derived growth factor alpha (PDGF-A), and their associated receptors, was downregulated, while factors known to enhance elastin production (TGF- α and TGF- β 1) were upregulated (Bland et al. 2008). Tropoelastin deposition is known to occur in response to mechanical stretch and hyperoxia, although curiously, the expression of elastin-regulating matrix proteins was not correspondingly increased. It is possible that enhanced tropoelastin expression and increased serine elastase activity in response to these stressors result in abundant but disorganized elastic fibers due to the absence of a concomitant increase in elastin-regulating proteins, ultimately leading to alveolar malformation (Bland et al. 2008).

Two essential modulator groups of ECM turnover are the matrix metalloproteinases (MMPs) and their natural regulators, tissue inhibitor of metalloproteinases (TIMPs). Presently, 24 MMPs

exist in humans, many of which are differentially expressed during the stages of lung development, although the significance of these patterns of expression has yet to be fully elucidated (Greenlee et al. 2007). They are capable of degrading a variety of targets, particularly ECM molecules such as collagen, which is indicative of their role in ECM remodelling during normal development and injury-induced repair (Greenlee et al. 2007). For example, the expression of MMP-2 and MMP-14 increases substantially at birth, while deletion of these genes is associated with abnormal alveolar development (Atkinson et al. 2005; Kheradmand et al. 2002). Conversely, altered levels of MMP and TIMP expression, as well as altered expression of other proteases, such as cathepsins, are a hallmark of inflammatory diseases, such as BPD (Altioik et al. 2006; Ambalavanan et al. 2008; Chetty et al. 2008; Schulz et al. 2004). Finally, with respect to the emerging concept of BPD involving a genetic predisposition (Abman et al. 2008), single-nucleotide polymorphisms of MMP-16 have recently been implicated in the protection against the development of BPD, although curiously, MMP-16 was elevated in a rat model of BPD (Hadchouel et al. 2008).

1.2.3.2 Growth Factors

The sites of secondary crest formation appear to be nonrandom, but instead arise from the deposition of elastin into the alveolar walls by myofibroblasts. One factor critical to the appropriate migration of myofibroblasts to the sites of secondary crest formation is PDGF-A (Bostrom et al. 1996; Lindahl et al. 1997). Myofibroblasts, or their precursors, respond to PDGF-A chemoattractant secretions from the epithelium by migrating to the peripheral sites of the lung and depositing elastin. Deletion of PDGF-A results in a dramatic reduction in elastin synthesis and consequently the absence of secondary crest formation (Lindahl et al. 1997). It has been proposed that PDGF-A expression is finely regulated by morphogen gradients which precisely localize migrating myofibroblasts to appropriate sites of septal initiation (Prodhan and Kinane 2002). Although the identity of the

morphogen involved has not been identified, candidate molecules include SHH and RA (Prodhan and Kinane 2002).

Critical roles for FGFs and their receptors, FGFR-1–5, have been demonstrated in both prenatal and postnatal lung development. During branching morphogenesis, FGF-7 and FGF-10 are expressed in the mesenchyme at areas of active branching, while FGFR-2 is complementarily expressed in the epithelium (Bellusci et al. 1997; Post et al. 1996). Furthermore, disruption of FGF-7, FGF-10, or FGFR-2 signalling through targeted deletion, antisense knockdown, or neutralizing antibodies results in diminished or absent branching, implicating the importance of reciprocal epithelial-mesenchymal interactions during morphogenesis (De Moerloose et al. 2000; Post et al. 1996; Sekine et al. 1999; Shiratori et al. 1996). Interestingly, dominant negative expression of FGFR-2 during embryonic, but not postnatal, lung development results in irreversible emphysema, which demonstrates how alveolarization can be indirectly impacted by dysregulation of proliferation or differentiation of precursors during the fetal period (Hokuto et al. 2003).

FGF signalling is also directly required for septation during alveolarization: double knock-out of FGFR-3 and FGFR-4 results in exuberant elastin deposition and consequently a failure of secondary septa to form, demonstrating the importance of interactions between soluble growth factors and the ECM (Weinstein et al. 1998). FGF-7 and FGF-2 are upregulated following hyperoxia-induced alveolar damage and may play a role in inducing reparative Type II to Type I cell transition (Buch et al. 1995). Furthermore, inhibition of FGF-2 signalling through FGFR-1 prevents normal postnatal rat lung cell apoptosis, while FGF-7 disruption reduces alveolar number (Padela et al. 2008; Yi et al. 2006).

FGF-7 is also an important stimulator of proliferation and maturation of developing Type II pneumocytes (Chelly et al. 1999) and is a positive predictor for absence of BPD in premature infants (Danan et al. 2002). FGF-7 also protects against injury caused by hyperoxia (Frank 2003) and/or mechanical ventilation (Welsh et al. 2000).

Interestingly, although FGF-7 did not prevent attenuated septation associated with hyperoxia (Welsh et al. 2000), exogenous FGF-7 stimulated compensatory lung growth following pneumonectomy by enhancing alveolar cell proliferation (Kaza et al. 2002). Finally, neonatal mice exposed to hyperoxic conditions during alveolarization display reduced FGFR-3, FGFR-4, and FGF-7 expression (Park et al. 2007).

Although TGF- β has received much attention for its function as a negative regulator of branching morphogenesis, it has more recently been implicated as an important factor in both alveolar formation and architectural maintenance (Alejandre-Alcazar et al. 2008). TGF- β suppresses Type II epithelial cell differentiation into Type I pneumocytes in human fetal cell culture, while it is downregulated upon glucocorticoid-induced differentiation (McDevitt et al. 2007). Interestingly, following an acute lung injury to Type I cells, Type II cells undergo phases of proliferation and differentiation, which are paradoxically suppressed and enhanced, respectively, by TGF- β (Bhaskaran et al. 2007). Disruption of TGF- β signalling resulted in emphysema-like air-space enlargement due to an abundance of matrix metalloproteinases, while conversely, introduction of excessive TGF- β led to pulmonary fibrosis, likewise indicating the importance of TGF- β regulation of ECM homeostasis (Bonniaud et al. 2004). TGF- β is also increased in the airway secretions of preterm infants with BPD (Kotecha et al. 1996). Moreover, enhanced TGF- β signalling and dysregulation of ECM-remodelling proteins are associated with hyperoxia-induced BPD in neonatal mouse models (Alejandre-Alcazar et al. 2007), while prenatal administration of a TGF- β -neutralizing antibody partially rescued the BPD phenotype (Nakanishi et al. 2007).

1.2.3.3 Transcription Factors

Despite the importance of transcriptional programs which mediate lung morphogenesis, transcription factors which regulate alveolarization specifically are not well described. Interestingly, many transcription factors which are critical for fetal lung development are downregulated during alveolarization. For example, GATA-6, despite

being important for branching morphogenesis, is not expressed postnatally, although postnatal GATA-6 overexpression in transgenic mice results in impaired alveolarization (Liu et al. 2003). Similarly, thyroid transcription factor-1 (TTF-1) is expressed in the epithelium of the fetal lung buds but becomes restricted to Type II cells postnatally (Wert et al. 2002). TTF-1 overexpression decreased alveolar septation and caused severe chronic pulmonary inflammation and Type II cell hyperplasia (Wert et al. 2002). In both cases, GATA-6 and TTF-1 appear to affect Type II to Type I cell differentiation with resultant impaired alveolarization if misexpressed.

It has long been known that inflammation, such as that experienced from maternal chorioamnionitis, accelerates lung maturation, although with an increased risk of the development of BPD (Watterberg et al. 1996). One link between them appears to be the well-characterized inflammatory transcription factor, nuclear factor κ B (NF- κ B), since NF- κ B epithelial overexpression appears to increase Type I and Type II cell number, possibly through decreased Type II cell apoptosis (Londhe et al. 2008). In contrast, neonatal deletion of the transcription factors forkhead box (Fox)a2 or homeobox protein (Hox)a5 leads to emphysema-like morphology due to impaired alveolarization (Mandeville et al. 2006; Wan et al. 2004). In both cases, characteristic features of inflammation were observed, including goblet cell hyperplasia, increased mucus production, and the recruitment of inflammatory cells.

Finally, mice deficient in the transcription factors estrogen receptor beta, Smad3, Foxf1, and CCAAT-enhancer-binding protein alpha all display defects in alveolar surface area and number due to a variety of causes, including Type II to Type I cell differentiation arrest and epithelial-mesenchymal signalling disruptions (Basseres et al. 2006; Chen et al. 2005; Kalinichenko et al. 2001; Patrone et al. 2003).

1.2.3.4 Retinoic Acid and Glucocorticoids

Adrenal glucocorticoids (GC), such as dexamethasone, are widely used to enhance late-stage fetal lung maturation and surfactant production

in premature infants, as well as postnatally as a treatment for neonatal respiratory distress syndrome. However, chronic exposure to GC during postnatal lung development has been found to have long-lasting adverse effects upon alveolar development (Tschanz et al. 2002). Rats exposed to dexamethasone during the first 2 weeks of life displayed impaired secondary crest formation and a consequent decrease in the alveolar number and parenchymal surface area, with such structural impairments lasting until at least early adulthood (Tschanz et al. 2002). GC-induced inhibition of septation has been associated with accelerated alveolar wall thinning, fusion of the double capillary layer (premature microvascular maturation), and impaired Type II to Type I pneumocyte differentiation (Massaro and Massaro 1986; Roth-Kleiner et al. 2005). In addition, GC appears to inhibit angiogenesis by downregulating VEGFR-2 (Clerch et al. 2004).

Interestingly, the administration of RA can at least partially rescue GC-induced alveolar deficiency (Clerch et al. 2004; Massaro and Massaro 2000). RA is the active metabolite of vitamin A (retinol) and is critical for both fetal and postnatal lung development: for example, retinol deficiency in weanling rats is associated with an emphysematous phenotype (Baybutt et al. 2000), while retinol levels in plasma and liver are deficient in very low birth weight neonates, particularly those which develop BPD (Shenai 1999). Intriguingly, administration of RA to adult mice can induce alveolar regeneration following dexamethasone- or elastase-induced emphysema, which is dependent upon FGF-mediated myofibroblast differentiation (Perl and Gale 2009).

RA treatment in rats enhanced alveolar septation and number in GC-treated rats (Massaro and Massaro 1996), while single deletions of its receptors, RAR- α , RAR- β , or RAR- γ , led to reductions in either alveolar number or gas-exchange surface area (Massaro et al. 2003; McGowan et al. 2000; Snyder et al. 2005). There may be a degree of compensatory redundancy in the RA receptors, since single-receptor deletions yield only modest—though distinct—pulmonary phenotypes, while overexpression of a dominant

negative RAR- α protein results in much more severe alveolar abnormalities (Yang et al. 2003).

Mechanistically, how RA and GC antagonistically interact to regulate alveolarization is not well described, although RA is known to increase expression of PDGF-A (Liebeskind et al. 2000) and FGF18 (Chailley-Heu et al. 2005) and to oppose the GC-induced downregulation of VEGFR-2 and midkine (Clerch et al. 2004; Kaplan et al. 2003). Deletion of RAR- β has also been shown to decrease PDGF-A protein, but not mRNA (Snyder et al. 2005). Finally, retinol uptake is disrupted in a rat model of nitrofen-induced congenital diaphragmatic hernia (CDH), while administration of RA to such rats enhances alveolarization and rescues lung hypoplasia, possibly by restoring Type II to Type I cell differentiation (Montedonico et al. 2008; Nakazawa et al. 2007; Sugimoto et al. 2008). These findings suggest that RA treatment may be able to improve or surmount impaired alveolarization caused by exposure to therapeutic hormonal administration or hyperoxic exposure in premature infants. However, vitamin A supplementation by itself has been shown to only modestly decrease the incidence of death or BPD in extremely low birth weight infants (Shenai 1999), indicating that our understanding of related factors involved in RA-mediated alveolarization is lacking.

1.2.4 The Pulmonary Vascular System in Alveolar Development

The dramatic changes in the pulmonary vasculature which occur during postnatal development have been termed “microvascular maturation.” This process involves extensive remodelling of the dual capillary layers flanking the developing septa in order to expand the distal lung vasculature. This occurs through several mechanisms, including the fusion of the dual capillary system into a monolayer, a concomitant reduction in connective tissue by the apoptosis of interstitial fibroblasts, and preferential growth of the microvasculature at defined capillary fusion sites (Caduff et al. 1986; Schittny et al. 1998). Perfused

vascular beds further create new capillaries by the process of microvascular intussusception, wherein existing vessels are extensively arborized by the formation of small transcapillary pillars which rapidly and effectively increase microvascular complexity without dramatic morphological remodelling (Burri et al. 2004; Caduff et al. 1986). The number of Type II cells is also reduced by both apoptosis and differentiation into Type I cells, thereby increasing the surface area and gas-exchange efficiency of the lung parenchyma (Schittny et al. 1998).

The mechanisms which control postnatal development of the pulmonary vasculature are not well described, in part because of the focus upon angiogenesis and vasculogenesis during fetal development. Much of the impetus for renewed interest in pulmonary vascular development arose from studies which demonstrated the critical links between vascularization and lung morphogenesis in both prenatal and postnatal development (DeLisser et al. 2006; Jakkula et al. 2000; Le Cras et al. 2002; McGrath-Morrow et al. 2005; Schwarz et al. 2000). These studies demonstrated that rather than being passive carriers of nutrients and blood gases, the developing vasculature is directly involved in promoting normal airway and alveolar growth and provides continued maintenance of the epithelial airways throughout postnatal life.

Thus, pulmonary vascular development continues postnatally, and likewise, disruption of the early postnatal pulmonary vasculature severely affects the normal formation of alveoli. Consequently, neonatal diseases such as RDS, BPD, and CDH, which feature lung hypoplasia and alveolar simplification, have been reexamined as being resultant from disrupted angiogenesis during critical periods of lung growth (Shehata et al. 1999; Thebaud and Abman 2007). Specifically, altered expression of the essential angiogenic growth factor, VEGF-A, and its associated receptors, VEGFR-1 and VEGFR-2, is a consistent characteristic of neonatal pulmonary diseases, including BPD, RDS, and CDH, and other diseases such as idiopathic pulmonary fibrosis (IPF) and acute respiratory distress syndrome (ARDS) in both humans and animal

models of these diseases (Asikainen et al. 2005; Bhatt et al. 2001; Cao et al. 2009; Chang et al. 2004; Farkas et al. 2009; Lassus et al. 2001; Maniscalco et al. 2005; Medford et al. 2009; Muehlethaler et al. 2008; Tambunting et al. 2005).

Further development of the concept that reduced alveolarization can result from dysmorphic vascular development comes from the recent report that in addition to decreased VEGF-A expression in the postmortem lungs of premature infants, the expression of a different class of angiogenic factor, endoglin, was increased (De Paepe et al. 2008). Endoglin is a regulatory component in the TGF- β signalling pathway and, hence, may be involved in a variety of morphological events, including endothelial cell proliferation and migration. This presents the idea that dysmorphic vascular growth may arise from two strikes: the overexpression of angiogenic factors largely uninvolved in normal alveolar development and the concordant reduction of established alveolar angiogenic factors, such as VEGF-A (De Paepe et al. 2008). In support of this, increased levels of another angiogenic factor, angiopoietin 2, in tracheal aspirates is also associated with the development of BPD (Aghai et al. 2008), while the administration of recombinant VEGF-A improves vascular function and development in experimental lung injury, although with some drawbacks, including enhanced fibrosis (Kunig et al. 2005, 2006; Medford et al. 2009; Thebaud et al. 2005).

Finally, evidence consistent with the idea that the pulmonary vasculature continues to perform essential maintenance of the alveolar structures throughout life comes from the transient knock-down of VEGF-A and interruption of VEGFR-2 signalling in adult mice and rats, respectively (Kasahara et al. 2000; Tang et al. 2004). Such interventions led to pruning of the pulmonary arterial tree and regression of the capillary beds, arising from endothelial cell apoptosis. More interesting, however, was the resultant increases in epithelial cell apoptosis, airspace enlargement, and increased compliance, all characteristic of emphysema, and which continued to manifest despite subsequent restoration of VEGF-A signalling. Although these interventions likely also

disrupted postulated autocrine VEGF-A signaling among the airway epithelium, it is possible that disruption of the pulmonary vascular bed in adulthood may also contribute to alveolar cell apoptosis and consequent pathogenesis long after lung morphogenesis has completed, echoing the results in the embryo and neonate.

1.2.5 Regulation of Postnatal Vascular Growth

VEGF-A has been the most extensively studied angiogenic factor in the context of the pulmonary vascular development. It is comprised of several splice variants with differential effects on endothelial function, particularly the isoforms VEGF₁₂₁, VEGF₁₆₅, and VEGF₁₈₉ in humans (rodent orthologues contain one less amino acid). Due to the alternative splicing of exons 6 and 7, VEGF-A isoforms differ in their ability to bind heparan sulfate proteoglycans: VEGF₁₂₁ is freely diffusible through the extracellular milieu, whereas the other isoforms possess increasing affinity for the heparan sulfate-rich ECM and are consequently less motile (Cross et al. 2003). The presence of distinct VEGF-A isoforms with different ECM affinities (and hence, different localized concentrations and distributions) during lung development suggests that each isoform may play distinct roles during pulmonary vascular development. All major VEGF isoforms are present in varying amounts during mouse lung development: during embryonic development, VEGF₁₂₀ and VEGF₁₆₄ are highly expressed relative to VEGF₁₈₈, possibly since the former two are more freely diffusible and consequently useful as endothelial chemoattractants during the formation of the early vascular plexus (Ng et al. 2001). In contrast, while total VEGF-A peaks following birth, VEGF₁₈₈ becomes the predominant isoform, while relative expression of VEGF₁₂₀ and VEGF₁₆₄ decreases after the second week of life, which may reflect the localized role of VEGF₁₈₈ in vessel maintenance (Ng et al. 2001). Indeed, VEGF-A isoforms have nonoverlapping roles in development since mice which express only VEGF₁₂₀ frequently die soon after birth due to ischemic cardiomyopathy, while

surviving mice exhibit poor pulmonary vascular growth (Carmeliet et al. 1999). Changes in VEGF-A isoform expression during lung injury may also be a contributing factor towards disease progression, since while total VEGF-A expression was increased in human ARDS samples, VEGF₁₂₁ and VEGF₁₆₅ (soluble isoforms) were decreased relative to VEGF₁₈₈ (cell-associated isoform) early but not later in the course of ARDS, perhaps due to isoform-specific repair mechanisms (Medford et al. 2009).

VEGF-A is a potent mitogen and chemoattractant produced and released primarily by the alveolar epithelium, particularly Type II cells, with paracrine effects upon the adjacent endothelium, which express the cognate receptors VEGFR-1 and VEGFR-2—also known as *fms*-like tyrosine kinase (Flt-1) and fetal liver kinase-1 (Flk-1), respectively (Raoul et al. 2004). There has been some suggestion that VEGF-A also has an autocrine effect upon Type II cell maturation or stimulation, although this appears to require indirect paracrine signalling from other cell types (Raoul et al. 2004).

While VEGF-A binds two receptor tyrosine kinases, VEGFR-1 and VEGFR-2, VEGFR-2 is thought to be the primary mediator of VEGF-A intracellular signalling, while VEGFR-1 appears to act mainly as a negative regulator of VEGF-VEGFR-2 interactions (Hiratsuka et al. 1998). VEGFR-1 null mice are embryonically unviable at the mid-somite stage due to defects in the organization of the vasculature, including exuberant formation of endothelial cells within the lumen of developing vascular structures (Fong et al. 1995). Hence, while VEGFR-1 is not required for endothelial cell differentiation, it is essential for the organization of the embryonic vasculature, possibly by regulating cell-cell or cell-matrix adhesion (Fong et al. 1995) or by sequestering VEGF-A from VEGFR-2 (Hiratsuka et al. 1998). In support of the sequestering model, a soluble form of the VEGFR-1 receptor is increasingly expressed in the developing lung endothelium (Yamamoto et al. 2007) and may act as a VEGF-A ligand decoy (Kendall and Thomas 1993). Antisense knockdown of VEGFR-2 in embryonic mouse lung explants resulted in severely impaired microvessel branching, while inhibition of VEGFR-1 enhanced the expression of VEGFR-2

and yielded increased and disorganized capillary networks, again suggesting that VEGFR-1 limits the extent of VEGF-VEGFR-2-mediated morphogenic events (Yamamoto et al. 2007). VEGFR-1 also has a much higher affinity for VEGF-A than VEGFR-2 despite lower kinase activity, while deletion of its kinase domain without interfering with ligand binding produces viable mice, strongly demonstrating that VEGF-VEGFR-1 intracellular signalling, per se, is not essential for vascular development (Hiratsuka et al. 1998).

Deletion of a single VEGF-A allele is embryonically lethal (Ferrara et al. 1996), while inhibition of postnatal VEGF-A signalling via neutralizing antibodies or small molecule inhibitors of angiogenesis inhibited alveolar septation and final alveolar number (Jakkula et al. 2000; Le Cras et al. 2002; McGrath-Morrow et al. 2005). Conversely, VEGF-A overexpression during alveolarization led to pulmonary hemorrhage, airspace remodelling, and emphysema (Le Cras et al. 2004).

VEGF is regulated by hypoxia-inducible factor 1 α (Hif-1 α), which, during hypoxia, transcriptionally activates and stabilizes VEGF-A mRNA, thereby enhancing vascular development. Conversely, the highly related Hif-2 α is postulated to regulate VEGF-A expression during normoxia (Hosford and Olson 2003). Interestingly, the hyperoxic BPD model in neonatal rats displays reduced expression of VEGF, VEGF receptors, and Hif-2 α (Hif-1 α was not assessed) (Hosford and Olson 2003), while in the baboon BPD model, both Hif-1 α and Hif-2 α were decreased (Asikainen et al. 2005). This directly relates the importance of environmental oxygen tension with VEGF regulation and, hence, pulmonary vascular development pre- and postnatally (Acarregui et al. 1999).

orchestrate normal alveolarization and how these pathways are disrupted in chronic lung diseases such as BPD are critical for the development of effective therapies.

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Essentials to Remember

Lung development is a complex multi-step process which is heavily dependent upon the precise orchestration of a variety of morphogenetic events. The identification of the fundamental regulators which

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The Neonatal Neuromechanical Unit: Generalities of Operation

2

Jacopo P. Mortola

Educational Aims

- General principles of operation of the neonatal respiratory system examined as a neuromechanical unit, that is, the translation of neural output into mechanical events, and the neurochemical feedback
- Implications of the highly compliant chest wall on the neonatal breathing pattern
- Dynamic elevation of the functional residual capacity: mechanisms and implications
- Importance of hypometabolism in neonatal hypoxia and its implications on the level of pulmonary ventilation

events accompanying birth. With respect to body size, the newborn's small body mass reduces the heat capacitance of the body and the high body surface-to-volume ratio favors heat loss. Hence, a large weight (W)-specific metabolic rate is required to offset the propensity for hypothermia. This translates into high values of oxygen uptake ($\dot{V}_{O_2}/kg$), which imply a proportionally large pulmonary ventilation ($\dot{V}_E$), achieved mostly by breathing at high rates. Indeed, fast breathing is a common characteristic of all newborn mammals. With respect to maturation, the development of the lung and respiratory apparatus is never completed at birth, even in the most precocial species. The lungs continue to grow postnatally, in a centripetal direction, with formation of peripheral airways and alveoli, implying that in newborns the central airways comprise a larger proportion of the total air space and contribute to a relatively large anatomical dead space. The incomplete myelination and low conduction velocity of neural fibers, including those of the laryngeal, vagi, and carotid sinus nerves, limit the afferent sensory information involved in the regulation of breathing. Finally, with respect to the adaptation to air breathing at birth, a multitude of events among the most dramatic of the whole life occur quite rapidly, such as the transition from filtration to absorption of the pulmonary fluid, the drastic changes in pulmonary circulation, and the rise in oxygenation with its implications on the function of the chemoreceptors.

This chapter touches on the general principles of operation of the neonatal respiratory system

2.1 Generalities

Many examples could be offered to illustrate the concept that the respiratory physiology of the newborn is markedly distinct from that of the adult. Some of the differences are determined by body size, others by the stage of development and maturation, and others yet by the tumultuous

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Table. 2.1 Terminology, abbreviations adopted in text, common units

Cw	Chest wall compliance	$\Delta\text{Volume}/\Delta\text{Pressure}$
CL	Lung compliance	$\Delta\text{Volume}/\Delta\text{Pressure}$
f	Breathing frequency	Breaths/min
FRC	Functional residual capacity	ml
P	Pressure	cm H ₂ O or mmHg
Pab	Abdominal pressure	cm H ₂ O
PaO ₂	Arterial pressure of oxygen	mmHg
PACO ₂	Alveolar pressure of carbon dioxide	mmHg
Pdi	Transdiaphragmatic pressure	cm H ₂ O
PEEP	Positive end-expiratory pressure	cm H ₂ O
Ppl	Pleural pressure	cm H ₂ O
T	Tension	dyne/cm
T _E	Expiratory time	s
T _I	Inspiratory time	s
V	Volume	ml
$\dot{V}$	Flow	ml/s
$\dot{V}_A$	Alveolar ventilation	ml/min
$\dot{V}_E$	Pulmonary ventilation	ml/min
$\dot{V}_{O_2}$	Oxygen consumption	ml/min
$\dot{V}_{CO_2}$	Carbon dioxide production	ml/min
V _r	Resting volume of the respiratory system	ml
V _T	Tidal volume	ml
W	Weight	kg

examined as a neuromechanical unit that operates to generate the optimal $\dot{V}_E$ responses by integrating peripheral information with metabolic requirements. The general principles of operation of the neuromechanical unit (that is, translation of neural output into mechanical events, evaluation of the adequacy of $\dot{V}_E$ from neurochemical feedback) are the same throughout the whole postnatal life. However, some functional aspects are peculiar to the neonatal period. The goal of this chapter is to highlight the functional properties characteristics of the newborn. References are not extensive, with preference given to review articles where the interested reader can trace the background information and technical details. A short list of terminology and abbreviations adopted in the text is given in Table 2.1.

2.2 Neural Output

The mechanisms involved in the generation of the neural output responsible for the breathing rhythm are still largely unexplained. Several approaches have attempted to unveil the origin of respiratory rhythmogenesis with reduced preparations, such as brainstem with or without the spinal cord or brainstem slices, commonly from neonatal rats. In vitro, it appears that a respiratory rhythm can be generated in very discrete brainstem regions (Haddad 2003), and the maturation of the putative respiratory centers has been studied extensively (Hilaire and Duron 1999). Nevertheless, discrepancies between the in vitro neural pattern and the natural breathing pattern in vivo are common and difficult to explain (Achard et al. 2005). Partly, these differences could be due to technical issues, adequate oxygenation of the preparation, and modification or abolition of the normal afferent inputs. Partly, they could reflect a fundamental flaw in the assumption that, normally, rhythmogenesis is independent of peripheral metabolic, neural, or chemical inputs. The major obstacle for a unifying interpretation of the results regarding the development of the neonatal network is the lack of an accepted model of respiratory rhythmogenesis.

What are the mechanisms that make breathing a continuous process at birth after the intermittent pattern of the fetal period is an unsolved mystery in perinatal physiology. The number and intensity of stimuli at birth – tactile, pressure, thermal, visual, and acoustic – are large. In addition, internal afferent inputs, like those of the chemoreceptors and of the airway mechanoreceptors, change markedly because of the rapid changes in oxygenation and in transpulmonary pressure. Under controlled experimental conditions, each of the putative stimuli in isolation can be shown to be important in initiating breathing. In fact, it is reasonable to assume that any stimulus can take a dominant role in specific situations (Jansen and Chernick 1991). Arousal, oxygenation, and a general state of stress (Lagercrantz and Slotkin 1986) increase metabolic rate, which by itself (through the increase in CO₂ production) stimulates breathing. Experiments on animal fetuses have indicated that exteriorization and clamping of the chord are not sufficient to trigger

and maintain continuous breathing unless also CO_2 is allowed to rise (reviewed in Mortola 2001). In birds, the trigger, increase, and maintenance of $\dot{V}_E$ at hatching are believed to be caused by the rise of metabolically produced CO_2 (Mortola 2009). Hence, it is quite possible that the risen level in metabolic rate at birth represents the main mechanism sustaining continuous $\dot{V}_E$.

In newborns, the phrenic output is typically an abrupt and short burst of activity with few spikes, quite different from the activity-reach ramp-shaped firing of the adult phrenic nerve. The rapid and short-lasting neural burst leaves little room for fine modulation. Presumably, this is one reason for the fact that in newborns peripheral inputs often play only a course control on the breathing pattern, which is typically irregular and variable. In fact, in the neonatal period peripheral neural afferents, despite being less in number and with lower firing frequency than in adults, can generate quite drastic reflex effects on breathing (2.5.1).

2.3 Translation of Muscle Contraction into Pulmonary Ventilation

The $\dot{V}_E$ generated by the contraction of the respiratory muscle results from three key steps (Fig. 2.1). First, the intrinsic mechanical characteristics of the muscle fibers determine the force

that the muscle is able to generate. Then, the force translates into pressure, the magnitude of which depends on the geometrical characteristics of the muscle and the structure over which the force is applied. Finally, the pressure generates airflow and causes changes in lung volume according to the flow-resistive and elastic properties of the respiratory system.

2.3.1 Step 1. Force Generation

For a long time it was suspected that the respiratory muscles of the newborn operate close to the fatigue threshold, as if they were barely capable to fulfill the ventilatory requirements. This view probably stemmed from the observation that breathing in neonates, especially premature infants, often is irregular and interspersed with periods of short apneas. The finding that the so-called “fatigue-resistant” muscle fibers were underrepresented fueled the idea that muscle failure was a contributor to periodic breathing and apneas (Keens et al. 1978; Le Souëf et al. 1988; Watchko et al. 1992; Vazquez et al. 1993). In reality, diaphragm fiber typing does not necessarily correlate with muscle fatigability (Sieck and Fournier 1991), and changes in diaphragmatic activity do not correlate with the infant’s periodic breathing or apneas (Nugent and Finley 1985). Studies on newborns of various species have shown the neonatal diaphragm to be at

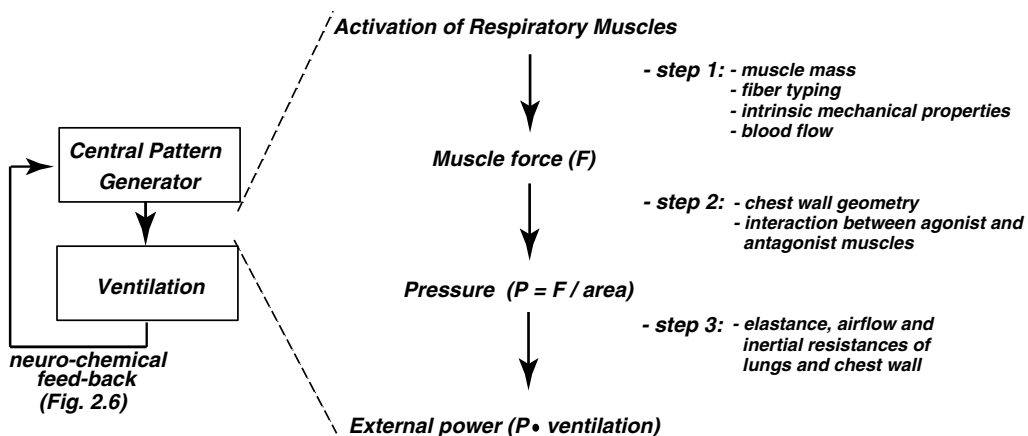


Fig. 2.1 Schematic representation of the neuromechanical unit for the operation of the respiratory system, with a generator, an output, and a feedback control. At right are

indicated the main steps involved in the translation of muscle activation into pulmonary ventilation

least as fatigue-resistant as the adult's diaphragm, capable of performing well even in the face of major workloads (Lieberman et al. 1972; Maxwell et al. 1983; Powers et al. 1991). Blood perfusion of the neonatal diaphragm is at least as adequate as it is in adult (Soust et al. 1989; Berger et al. 1994), even at high contraction rates or against resistive loads.

2.3.2 Step 2. Pressure Generation

In mammals, the total mass of the respiratory muscles, in relation to body mass, is almost a fixed proportion irrespective of species and animal age. The force produced by a muscle is proportional to its cross-sectional area, and the resulting pressure is the ratio between the force produced and the surface which the force is applied on. Because of their small size, the neonatal respiratory muscles produce little force by comparison to adults (Sieck et al. 2002). However, the surface over which such force is applied is proportionally small; hence, mammals of all sizes and ages do not differ much in the pleural pressure that their respiratory muscles can generate (Mortola 2001).

The shape of the diaphragmatic dome is an additional factor in the translation of force into pressure. In fact, by application of the Young-Laplace relationship, for a given diaphragmatic tension T , the resulting transdiaphragmatic pressure P_{di} ¹ depends on the radius of curvature r of the dome ($P_{di} = T/r$). In newborns, the fact that r is much smaller than in adults favors the generation of a greater P_{di} for a similar T . In conclusion, despite the fact that muscle mass and muscle force are undoubtedly less in newborns than in adults, the tidal swings in pleural pressure (P_{pl}) are similar at all ages, about 5–7 cm H₂O.² If needed, the healthy newborn can generate much higher P_{pl} values, up to 100 cm H₂O, as is the case during the

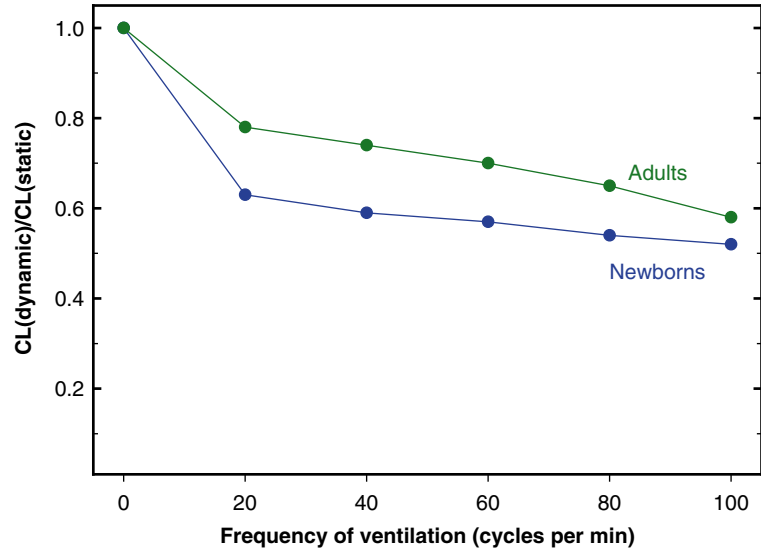
first inspiration (Mortola 2001). The infant's maximal inspiratory pressures during crying (Shardonofsky et al. 1989) are not much lower than the maximal static inspiratory pressures developed by adults.

Contraction of the diaphragm raises abdominal pressure (P_{ab}). This increase causes the outward motion of the frontal abdominal wall during inspiration and the expansion of the lower portion of the rib cage. The latter occurs because of the mechanical interdependence between the abdomen and rib cage and because P_{ab} gets transmitted to the thoracic wall through the apposition area. The apposition area is the lowermost region of the rib cage that the diaphragmatic dome faces without interposed lungs. In infants, differently from the adult, in inspiration the expansion of the lower rib cage is small because of two reasons. First, the high abdominal compliance limits the rise in P_{ab} during diaphragmatic contraction. Second, the rather rounded shape of the ribs and their almost perpendicular attachment to the vertebral column limit the size of the area of apposition (Allen and Gripp 2002). With growth, the area of apposition increases because of the gradual downward orientation of the ribs, presumably caused by the gravitational pull. The result of this anatomical arrangement is that in newborns the increase in P_{ab} during diaphragmatic contraction does not contribute to the expansion of the lower ribs as much as it does in adults. Switching from the supine to the prone position stiffens the abdomen; in fact, this postural change is functionally equivalent to binding the infant's abdomen and improves diaphragmatic efficiency (Fleming et al. 1979; Guslits et al. 1987; Laing et al. 1988; Wolfson et al. 1992) with positive effects on blood oxygenation (Numa et al. 1997). As an aside, it is interesting to note that the sudden infant death syndrome (SIDS) has a greater prevalence in the prone position (Silvestri and Weese-Mayer 2003). This implies that in the prone position the posture-related factors involved in the physiopathology of SIDS, whatever they may be, more than offset the advantage in the mechanical operation of the respiratory system.

¹ P_{di} is the pressure difference between the abdomen and the pleural space, or $P_{ab} - P_{pl}$.

² For analogous reasons, the tidal pleural pressure swings have similar values in species of very different body size.

Fig. 2.2 An example of dynamic lung compliance progressively lower than the static value the higher the frequency of ventilation. The phenomenon, often labeled “frequency dependence of compliance,” is contributed by the stress relaxation of the pulmonary structures and by peripheral resistance. These experimental data refer to newborn and adult cats (Redrawn from the data of Sullivan and Mortola (1986))



2.3.3 Step 3. Lung and Chest Wall Mechanics

As it is the case for many other internal organs, the W-specific mass of the lung (lung weight-body weight ratio) is large in newborns and decreases during postnatal growth. Despite the large mass, air spaces are still incompletely developed, the pulmonary elastin and collagen contents are low, and during the first postnatal hours or days, some fluid is trapped in the peripheral airways and lung interstitium. All these factors contribute to values of lung compliance (CL, $\Delta\text{volume}/\Delta\text{pressure}$) lower in newborns than in adults, when the comparison is made on the basis of lung volume or lung weight. The peripheral inequalities in airway resistance and the viscous properties of the pulmonary tissue prolong the response time of the lungs both in inspiration and in expiration. For these reasons, the differences between dynamic and static CL (and, possibly, the phenomenon of frequency dependence of CL³) are more pronounced in newborns than in adults (Fig. 2.2).

The chest wall anatomically and functionally comprises two main compartments, the rib cage (or thorax) and the abdomen-diaphragm. Chest wall compliance (Cw) has been measured in

newborns of many species and in infants; the results have been uniform in revealing high values (after normalization by body W) in comparison to the adult. The high Cw in newborns is a structural necessity for the passage through the birth canal. Cw decreases gradually during postnatal growth (Papastamelos et al. 1995), probably because of the stiffening of the cartilaginous structures and changes in abdominal and thoracic configuration.

Because the Cw-CL ratio is a dimensionless parameter, it can be compared directly among individuals of different age or body size, with no needs for normalization. In adult humans, because Cw and CL have similar values, their ratio is approximately equal to one. In infants, Cw is about five times higher than CL (Polgar and Weng 1979). In fact, the high Cw-CL ratio is a characteristic feature of the respiratory system of all neonatal mammals investigated (Mortola 2001). The fact that Cw is so high relative to CL implies that in infants CL is the major determinant of the compliance of the respiratory system (Crs) and that changes in Crs are an excellent indicator of changes in CL. From a practical viewpoint, this is quite convenient because measurements of CL in infancy can be difficult (due to the uncertainties in the measurements of Ppl), while measurements of Crs can be performed easily (England 1988; Wohl 1991; Mortola 2004).

³ Whereby CL decreases, the faster the ventilation rate.

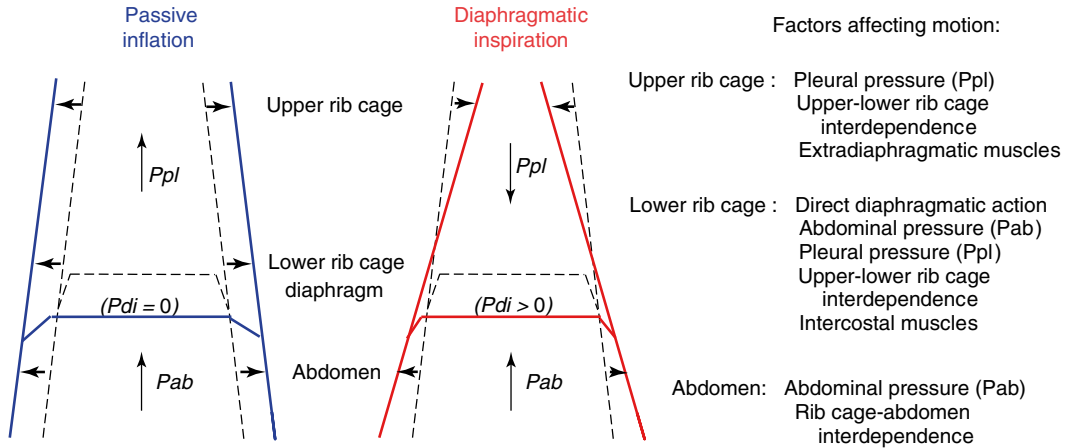


Fig. 2.3 Schematic representation of the two main compartments of the chest wall (*dashed line*), the rib cage and abdomen, separated by the diaphragm. During passive inflation (*panel at left*), the pressure across the diaphragm (transdiaphragmatic pressure, P_{di}) is zero because the diaphragm is relaxed. In this condition, pleural pressure

(P_{pl}) and abdominal pressure (P_{ab}) increase by similar amounts, and both compartments expand. When the diaphragm contracts ($P_{di} > 0$, *panel at right*), P_{ab} increases and P_{pl} decreases. The result is that the abdomen expands while the rib cage moves little in its lower portion and caves inward in its upper portion

2.4 Mechanical Constraints and Breathing Pattern

The high Cw-CL ratio of the newborn has two major implications. First, in inspiration, the tendency of the chest wall to distort is greater than in adults. Second, during expiration, the low ratio reduces the outward pull of the chest on the lungs and facilitates lung emptying and a low resting volume of the respiratory system (V_r). These mechanical characteristics have an impact on the neonatal pattern of breathing.

2.4.1 Chest Wall Distortion

In any solid structure, distortion can be defined as a configuration that differs from that requiring minimal energy. In the case of the chest wall, distortion occurs in active conditions (i.e., during respiratory muscle contraction) when the shape deviates from the configuration assumed in the passive situation.⁴ This latter is the configuration

attained at any lung volume when the respiratory muscles are relaxed, as is the case, for example, during mechanical ventilation. By definition, the occurrence of distortion implies that the respiratory muscles need to spend extra energy to generate a given tidal volume (V_T). In inspiration, distortion is the unavoidable consequence of the location of the diaphragm between the two main chest wall compartments, the abdomen and thorax. In fact, during contraction (i.e., with $P_{di} > 0$) the diaphragm operates simultaneously as a positive pressure pump for the abdomen, raising P_{ab} , and as a negative pressure pump for the thorax, lowering P_{pl} . Therefore, differently from the passive inflation in which P_{ab} and P_{pl} rise homogeneously and expand both abdomen and thorax, during active inspiration the abdomen expands while the rib cage caves inward (Fig. 2.3). The suction on the rib cage can be appreciated visually in tetraplegic patients, who have no control of the extradiaphragmatic muscles (Mortola and Sant'Ambrogio 1978; Thach et al. 1980). In normal conditions, the tendency to distortion is less in adults than in newborns because adults have a more rigid chest wall and greater compensatory action of the extradiaphragmatic muscles. In newborns, the highly compliant chest wall, the small area of apposition (2.3.2), and the limited mechanical linkage between lower and upper rib

⁴The terms *active* and *passive*, *static* and *dynamic*, refer to the modes of operation of the respiratory system. *Active* and *passive* indicate, respectively, the presence or absence of respiratory muscle contraction. *Static* and *dynamic* indicate, respectively, the absence or presence of airflow.

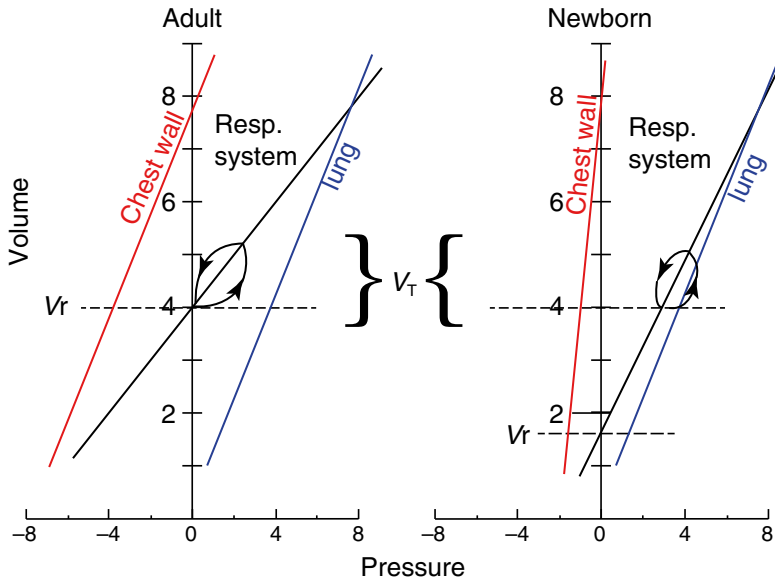


Fig. 2.4 Schematic pressure-volume (P-V) relations of the lungs, chest wall, and respiratory system (*heavy line*) in adult (*left*) and newborn (*right*). For simplicity, the P-V relations are indicated by *straight lines*, the slope of which represents the compliance. At left, the compliance of the chest wall (Cw) is similar to that of the lungs (CL). At right, the Cw-CL ratio is about five times higher. The

result is that in the newborn the resting volume of the respiratory system (V_r , *dashed line*) is lower than in adults. Tidal volume (V_T , with inspiratory-expiratory loops indicated by *arrows*) is approximately at the same absolute lung volume in both newborns and adults, because newborns keep their end-expiratory level dynamically elevated

cage are the main factors responsible for chest distortion, of which the most obvious aspect is the paradoxical inward motion of the rib cage during inspiration and expansion in expiration. In addition, the poor activity and mechanical coordination of the intercostals muscles, especially during some phases of sleep (Muller et al. 1979), further contribute to the limited stability of the neonatal thorax.

It is difficult to estimate the energetic price of distortion. Taking the abdominal expansion as an index of diaphragmatic shortening during inspiration, in newborns during resting breathing, chest wall distortion reduces by half the inspiratory efficiency of the diaphragm (Mortola 1995). This means that, in first approximation, to achieve a given V_T , the diaphragm must contract twice as much than it would need had the system expanded along its passive configuration. An additional burden caused by chest distortion is the deformation of the lungs, which reduces CL (Sullivan and Mortola 1985) and probably worsens the ventilation-perfusion matching. As mentioned above (3.2.), the prone position, by stiffening the chest wall, reduces its distortion

during inspiration and improves the mechanical efficiency of breathing.

2.4.2 Low Resting Volume: Problems and Solutions

A highly compliant chest wall exerts a lesser outward pull on the lungs than a stiffer chest does, with the result that the passive resting volume of the respiratory system (V_r , the volume at which lungs and chest recoil pressures offset each other) is low (Fig. 2.4). Indeed, V_r (after normalization by lung weight) is lower in newborns than in adults of several species and in infants by comparison to the adult man (Cook et al. 1958; Fisher and Mortola 1980). The fact that V_r is low carries consequences on the functional residual capacity (FRC), which has a prominent role in the efficient operation of the mammalian respiratory system. FRC buffers the oscillations and maintains the stability of the alveolar and arterial gases and is a reserve of oxygen during occasional periods of hypoventilation or apneas. Most important is the fact that inflation of the lungs

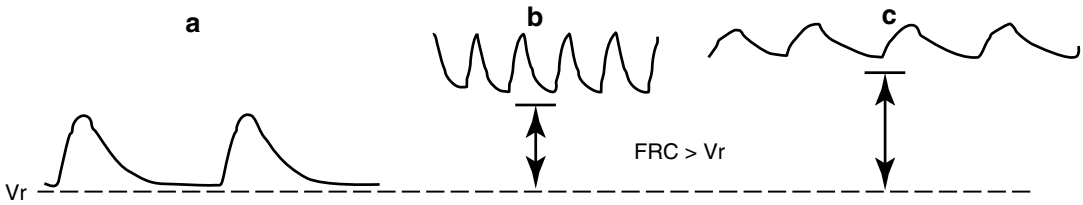


Fig. 2.5 Schematic representation of the dynamic elevation of the end-expiratory level (FRC). (a) represents the breathing pattern with expiration ending at resting volume (V_r); this is the common resting pattern of adult

humans. (b, c) Represent patterns commonly seen in infants, in whom FRC is above V_r because of fast breathing (b) or because of laryngeal expiratory braking (c)

from FRC requires substantially less pressure than inflation from a collapsed state. In adults during resting breathing, FRC is essentially equal to V_r . Infants, on the contrary, compensate the potentially disadvantageous mechanical situation of the low V_r by keeping FRC dynamically elevated; hence, differently from adults, in infants FRC exceeds V_r (Fig. 2.4).

The core mechanism that permits a dynamic elevation of FRC above V_r is a mismatch between the time needed for expiratory flow (mechanical expiratory time) and the neural expiratory time (T_E), with the former being longer than the latter. In this way, inspiration begins before the air is fully exhaled, causing lung hyperinflation. At least three mechanisms operate to achieve this goal, the post-inspiratory activity of the expiratory muscles, laryngeal braking in expiration, and high breathing frequency (Fig. 2.5). The former two prolong the mechanical T_E and the latter shortens the neural T_E . All of them are operative, either together or individually, in infants (Eichenwald and Stark 2003) and in newborns of many other species (Mortola 2001). In infants, the $FRC - V_r$ difference is 10–15 ml, or about 3 ml/kg. In cases of apnea (long neural T_E) FRC invariably decreases toward V_r . During mechanical ventilation, the presence of an endotracheal tube eliminates the newborn's laryngeal control of expiratory flow; in this case, the application of an end-expiratory load (or positive end-expiratory pressure, PEEP) of a few cm H_2O is necessary to counteract the otherwise unavoidable drop in FRC. This becomes even more necessary in conditions of low CL because of lung disease, which further increases the Cw-CL ratio (Gregory et al.

1971; Berman et al. 1976). In fact, the $FRC - V_r$ difference can be seen as a mechanism that generates an internal PEEP of a few cm H_2O . Although small, this positive airway pressure probably contributes to the absorption of the pulmonary fluid from the alveolar spaces into the lung interstitium during the first hours after birth (Strang 1991).

2.5 Feedback Regulation

Because gas exchange is the primary purpose of breathing, O_2 and CO_2 chemoreceptors could be considered sufficient to provide the pertinent information about the function of the neuromechanical unit (Fig. 2.1). However, although essential, the information on blood gases is not adequate for immediate responses to perturbations on breathing, because of the long delay built in the chemoreceptor feedback system. In fact, chemical feedback operates on a time scale of minutes and is most effective in managing the proper matching between alveolar ventilation ($\dot{V}_A$) and metabolic requirements. A separate and purely neural feedback provides instantaneous information on the status of lung expansion, with reflex responses operational within the breath itself (Fig. 2.6). Some of this feedback originates from airway mechanoreceptors (pulmonary stretch receptors), specifically concerned with the status of lung expansion.⁵ Proprioceptors within the respiratory muscles provide additional

⁵The tension in the airway wall is the stimulus for these receptors.

recurrent laryngeal nerve, which is important in the control of FRC (2.4.2), and the efferent control of airway smooth muscle, with effects on the activity of the airway receptors (Fisher et al. 2003). In addition, the vagal pulmonary innervation influences the secretion of surfactant and lung compliance.

In newborns, the activity of the pulmonary airway receptors at end expiration and during lung expansion is less than in adults (Fisher et al. 1991). Many neural fibers are of small diameter and are not myelinated, with low conduction velocity (Schwieler 1968; Marlot and Duron 1979; Hasan et al. 1993). As mentioned above (2.2), during the neonatal period the combination of a limited peripheral afferent input with a strong reflex response is not infrequent, and the pulmonary vagal reflexes are one example of this combination. Hypoxia and hyperthermia, either singly or combined, strengthen the vagal reflex inhibition of breathing, a phenomenon that could have some importance in the genesis of breathing irregularities (Mortola 1999).

2.5.2 Extrapulmonary Ventilatory Reflexes

From studies in adult humans and animals, it is clear that stimuli from the most disparate sources – internal (e.g., carotid sinus, bladder and abdominal viscera, nasal, pharyngeal, and laryngeal regions) and external (e.g., visual, tactile, thermal, auditory) – can have reflex effects on breathing. Out of this multitude of extrapulmonary ventilatory reflexes, only a few have been studied with sufficient depth in the neonatal period.

The upper airways are involved in multiple functions; in newborns, reflexes from this area exert mostly inhibitory influences on breathing. Experiments on neonatal mammals have shown that liquids instilled in the pharyngolaryngeal area trigger apneas and bradycardia, the severity of which decreases with postnatal growth. Small $[Cl^-]$, high $[K^+]$, and extreme deviations of the pH of the liquid cause the strongest episodes of apnea (Boggs and Bartlett 1982). Observations in infants, although very limited (Plaxico and

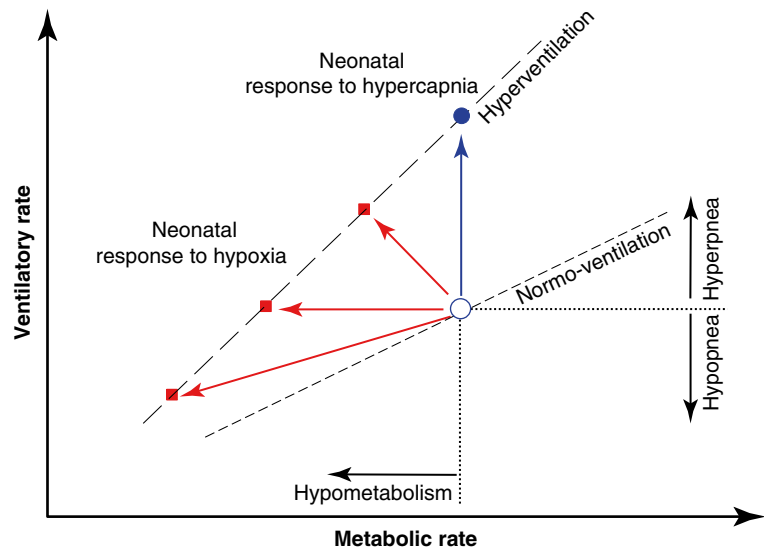
Loughlin 1981; Davies et al. 1989; Wennergren et al. 1989), suggest that the results in animals are applicable to the human case and may be part of the reflexes lowering $\dot{V}_E$ during oral feeding (Mathew 2003). Cooling of the laryngeal mucosa or sustained negative pressures in the upper airways are other powerful inhibitory stimuli on breathing (Fisher et al. 1991), responsible for reflex apneas that can persist beyond the removal of the stimulus. The evolutionary significance of the ventilatory inhibition triggered by upper airway reflexes is unclear. The inhibition of breathing may be considered the most obvious response against foreign bodies in the upper airways, irritants, or gastroesophageal reflux. The associated reflexes designed to clear the upper airway passages, like sneezing, coughing, and other responses common in adults, in newborns have modest efficacy (Mortola and Fisher 1988; Chernick 2002).

Gentle touching of the skin can facilitate breathing; presumably, this is one purpose for the maternal grooming and licking of the pups at birth practiced by many mammals. In humans, the skin-to-skin contact between infant and mother (“kangaroo care”) seems to reduce apneas and increase the regularity of the breathing pattern (Anderson 1991). However, the reflex response to skin stimulation is not necessarily facilitating breathing, since inhibitory effects, including apnea, have been described (reviewed in Mortola 2001). The large range of responses probably reflects the interplay of numerous factors of difficult control in an experimental setting, the intensity and location of the stimulus, association with other inputs, metabolic condition, state of alertness or sleep stage, etcetera. It seems probable that under normal circumstances, inputs from the chest wall have low priority on the regulation of breathing by comparison to inputs from the lungs and the chemoreceptors.

2.5.3 Chemical Feedback

The O_2 and CO_2 chemoreception important for respiratory control is organized at two sites, the arterial blood (carotid body) and the ventral

Fig. 2.7 Metabolism-ventilation diagram. The oblique *short-dashed line* joins various combinations of metabolism and ventilation during normo-ventilation, of which the open circle represents one case. Hyperventilation is the increase in the ventilation-metabolism ratio, as represented by the steeper *long-dashed line*. In newborns, hypercapnic hyperventilation (*filled circle*) is obtained by an increase in $\dot{V}_E$ (hyperpnea) with no hypometabolism. Differently, hypoxic hyperventilation is obtained by various combinations of hypometabolism and hyper- or hypopnea (*squares*)



surface of the medulla in close contact with the respiratory neurons. Only the former senses changes in oxygenation by monitoring the arterial partial pressure of O_2 (PaO_2). With some variations, this arrangement is common at all mammals and ages; however, the degree of operation of the receptors and their ventilatory reflexes differ between newborns and adults.

2.5.3.1 Hypoxia

The ventilatory response to hypoxia during the early postnatal period has been the object of extensive investigation after the earliest observations that in newborn infants the hypoxic increase in $\dot{V}_E$ is minimal by comparison to adult humans. In fact, during hypoxia $\dot{V}_E$ can even drop below the normoxic value (e.g., Brady and Ceruti 1966; Cohen et al. 1997; Horne et al. 2005). These results have been confirmed on a large number of neonatal species. The interpretation of the $\dot{V}_E$ response to hypoxia is complex (Mortola 1996; Powell et al. 1998). In newborns, a major factor is the metabolic response to hypoxia, usually quantified as a change in oxygen consumption ($\dot{V}_{O_2}$). Measurements in infants (Brady and Ceruti 1966; Rigatto and Brady 1972) and in neonatal animals have shown that arterial PCO_2 does not increase in hypoxia even when $\dot{V}_E$ is below the normoxic level. The only explanation is that the drop in $\dot{V}_E$ is accompanied by a parallel decrease

in metabolism.⁶ In fact, many studies have indicated that newborn mammals drop $\dot{V}_{O_2}$ during hypoxia, as reported first in human infants (Cross et al. 1958). Hyperventilation, defined as an increase in the ventilation-metabolism ratio and expressed by the drop in alveolar or arterial PCO_2 , equally results from hyperpnea (increase in $\dot{V}_E$) or hypometabolism (drop in $\dot{V}_{O_2}$), in any combination (Fig. 2.7). In adult humans the hyperpnea represents the common way to hyperventilate; in newborns, hypometabolism is the main mechanism to achieve hypoxic hyperventilation, usually with minimal hyperpnea (Mortola 1999). The hypometabolism results from the downregulation of various energy-consuming functions, especially thermogenesis (with a drop in body temperature) and body growth. The benefit of hypoxic hypometabolism is a hypoxic resistance far superior to adults. The physician's failure to recognize hypometabolism as the key strategy adopted by the newborn to cope with hypoxia can lead to unnecessary or mistaken interventions on the infant's ventilation and body temperature.

⁶In fact, $PaCO_2$ is in equilibrium with the alveolar pressure of CO_2 ($PACO_2$), which, for a given barometric pressure P_b , is solely determined by the ratio between CO_2 production ($\dot{V}_{CO_2}$) and alveolar ventilation ($\dot{V}_A$), according to the alveolar gas equation $PACO_2 = (\dot{V}_{CO_2} / \dot{V}_A) \cdot P_b$.

Recordings from neural afferent fibers of the carotid sinus nerve or from its cell bodies in the sensory petrosal ganglion have indicated that the carotid body is tonically active in newborns and probably in the fetus (Mulligan 1991). However, neither the tonic activity at resting PaO_2 nor the carotid body neural afferent response to hypoxia or hypercapnia is as marked as at older ages (Carroll et al. 1993). During maintained hypoxia, the excitation of the carotid sinus nerve is sustained over time, even when the ventilatory output is declining; this indicates that the modest or absent hyperpnea of the hypoxic newborn cannot be attributed to adaptation of the chemoreceptors. Hyperoxia lowers or completely silences the tonic activity of the carotid body. The rapid oxygenation at birth in the transition from the fetal to postnatal life probably saturates the chemoreceptors and silences them temporarily, until they gradually reset to the postnatal value of PaO_2 .

Chemodenervation, either surgically or functionally induced by hyperoxia, reduces $\dot{V}_E$ and causes irregularities in breathing. Whether or not the absence of this peripheral chemo-feedback in the newborn results in severe respiratory insufficiency and eventually death is unclear; in fact, experimental studies have produced conflicting results (reviewed in Mortola 2001).

2.5.3.2 Hypercapnia

All newborn species investigated respond to hypercapnia with hyperpneic hyperventilation (absolute increase in $\dot{V}_E$, Fig. 2.7), although the postnatal temporal evolution of the response may vary from species to species (Putnam et al. 2005). The neonatal hypercapnic response has two qualitative differences from the hypoxic response. First, the hyperventilation is entirely contributed by the hyperpnea even in those newborns that do not increase $\dot{V}_E$ in hypoxia, with minimal changes in $\dot{V}_{\text{O}_2}$. Second, the hyperpnea is characterized predominantly by an increase in V_T in both animals and human infants (Brady and Dunn 1970; Haddad et al. 1980; Martin et al. 1985; Mortola and Lanthier 1996), contrary to the shallow and rapid breathing of the response to hypoxia.

After peripheral chemodenervation, the $\dot{V}_E$ response to CO_2 is still present, meaning that the chemoreceptors located centrally close to the medulla are functional (Purves 1966). Other approaches, on the whole animal or in reduced preparations, have confirmed that the central chemosensory areas are active in the newborn and that are responsive to changes in CO_2 and pH (Wolsink et al. 1991; Issa and Remmers 1992; Wennergren and Wennergren 1980, 1983; Whittaker et al. 1990). With CO_2 exposure, neurons expressing Fos-protein, taken as a marker of the immediate early gene c-Fos, were found in the ventrolateral medulla of neonatal rats; the incidence of these neurons was not lower than in older rats (Belegu et al. 1999). All together, these and other observations indicate that the central chemosensory area is active since birth and probably in the late fetal phases (Nattie 1991) and that the $\dot{V}_E$ response to its stimulation is, at least qualitatively, similar to the adult.

Conclusions

As mentioned at the onset of this chapter, respiratory physiology in the neonate differs from that of the adult in many aspects intertwined in a complex web. Any arbitrary attempt to point at just a few of them is bound to be restrictive and superficial. Nevertheless, after having focused our attention to the generation of mechanical output and the feedback operation, in the opinion of this author, the most fundamental peculiarities of the neuro-mechanical unit in the neonatal period can be summarized as follows:

- (a) The high C_w (and high C_w -CL ratio) is a functional characteristic responsible for the low V_b , with consequences on inspiration (chest distortion and extra inspiratory work) and expiration (dynamic elevation of FRC).
- (b) The low number of myelinated fibers (small conduction velocity) in the vagus, laryngeal, and carotid sinus nerves limits the effectiveness of peripheral feedback control.
- (c) The abrupt and brief burst of neural output activity contributes to the fact that changes

in feedback information produce rather course changes in amplitude and duration of inspiration. This could contribute to the variable breathing pattern and to the apparent paradox that in newborns, despite (b), peripheral inputs can provoke dramatic effects on $\dot{V}_E$.

- (d) During hypoxia, the hypometabolism is a neonatal strategy of fundamental importance and great effectiveness. It has implications on the control of the set point of body temperature and permits adequate hyperventilation with minimal hyperpnea.

Essentials to Remember

- In infancy, chest wall compliance (Cw) relative to lung compliance (CL) is higher than in adults. A useful practical consequence is that measurements of the compliance of the respiratory system (which can be performed easily both during spontaneous breathing and mechanical ventilation) are excellent indicators of CL.
- During mechanical ventilation, the presence of an endotracheal tube eliminates the newborn's laryngeal control of expiratory flow; in this case, the application of an end-expiratory load (or positive end-expiratory pressure) of a few cm H₂O is necessary to counteract the otherwise unavoidable drop in end-expiratory volume. This becomes even more necessary with lung diseases that lower CL and further increase the Cw-CL ratio.
- In the neonatal period, peripheral neural afferents, despite being less in number and with lower firing frequency than in adults, can generate drastic reflex effects on breathing. During mechanical ventilation, reflex inhibition on inspiration originates from the distention of the lungs and central airways, especially at elevated PEEP. The reflex inhibition on

breathing may be desirable to eliminate infant-ventilator interaction, but may be misleading in assessing the infant's capacity for spontaneous breathing.

- Liquids instilled in the pharyngolaryngeal area trigger apneas and bradycardia, especially at the youngest ages.
- In newborn infants, hypoxia decreases metabolic rate much more readily than it does in adults. This metabolic drop lowers the inspiratory output and the level of pulmonary ventilation and is often accompanied by a decrease in thermogenesis and body temperature. Failure to recognize hypometabolism as the key strategy adopted by the newborn to cope with hypoxia can lead to unnecessary or mistaken interventions on the infant's ventilation and body temperature.

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David A. Turner and Ira M. Cheifetz

Educational Aims

- Understand the physiology of alveolar ventilation.
- Understand the relationship between alveolar ventilation and oxygenation.
- Review the alveolar gas equation.
- Understand the distribution of blood flow and ventilation in the lung.
- Assess the impact of intrapulmonary shunts and dead-space ventilation on gas exchange.
- Review the principles of gas diffusion.
- Understand the physiologic principles of oxygen transport and delivery.
- Understand the relationship between oxygen delivery and consumption.
- Review the interpretation of arterial and venous blood gases.

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3.1 Pulmonary Gas Exchange

The ultimate goal of pulmonary gas exchange is adequate tissue oxygen (O_2) delivery and carbon dioxide (CO_2) elimination. This exchange of gas is a multistep process that begins with ventilation and movement of gas from the atmosphere through the various generations of airways into the alveoli of the lungs. Oxygen quickly diffuses across the alveolar-capillary membrane into red blood cells (RBCs), allowing for transport of O_2 to the tissues. The final step in gas exchange occurs in the tissues as oxygen diffuses into cells to meet the metabolic demands of the body. Similarly, CO_2 diffuses from the cells into RBCs at the tissue level and is transported to the alveolar capillaries to be exhaled into the atmosphere.

Given the multiple steps involved in gas exchange for both O_2 and CO_2 , there are a number of points in which this process may become disrupted. Despite the complexity of this process, pulmonary gas exchange is generally remarkably effective. This process usually leads to the adequate elimination of CO_2 and to the delivery of O_2 to tissues and organs well in excess of the body's metabolic demands.

3.2 Alveolar Ventilation and Alveolar PO_2

The initial step in gas exchange is adequate pulmonary ventilation. Ventilation is ultimately controlled by the amount of gas that reaches the

alveolar-capillary interface to participate in gas exchange. Each inhalation contains a specific volume of gas, but a portion of this inspired volume is not available for gas exchange since it does not pass beyond the conducting airways. Gas that remains in the conducting airways at the end of inspiration represents the anatomic dead space. This anatomic dead space in combination with any additional alveolar dead space related to lung pathology or mechanical ventilation comprises total physiologic dead-space ventilation (Numa and Newth 1996; Nunn et al. 1959).

Dead-space ventilation has a direct impact on alveolar ventilation. The total quantity of alveolar ventilation is the amount of gas, summed over 1 min, which reaches the capillary bed to potentially participate in gas exchange. Alveolar ventilation is, thus, calculated by subtracting the anatomic dead-space volume from the total inspired volume. The quantity of gas that actually participates in gas exchange is calculated by subtracting the total dead space (anatomic plus alveolar dead space) from the total inspired volume (West 2005a; Numa and Newth 1996; Nunn et al. 1959).

Alveolar ventilation contributes primarily to gas exchange through the control of CO₂ elimination. CO₂ elimination is determined by the balance between CO₂ production and alveolar ventilation. For a constant level of CO₂ production, CO₂ elimination is inversely proportional to alveolar ventilation. In healthy subjects, the partial pressure of alveolar CO₂ ($P_A\text{CO}_2$) closely approximates the partial pressure of arterial CO₂ ($P_a\text{CO}_2$). As alveolar ventilation increases, CO₂ elimination increases, and $P_A\text{CO}_2$ (and consequently $P_a\text{CO}_2$) falls. Adequate CO₂ elimination not only prevents respiratory acidosis and acidemia, but also significantly impacts alveolar oxygen levels. The relationship between the partial pressure of alveolar oxygen ($P_A\text{O}_2$) and $P_a\text{CO}_2$ is a complex one that includes a number of components. This relationship is reflected in the alveolar gas equation as follows:

$$P_A\text{O}_2 = P_I\text{O}_2 - P_a\text{CO}_2 / R$$

In this equation (the alveolar gas equation), $P_A\text{O}_2$ represents the alveolar partial pressure of oxygen. Additional variables are defined as follows:

- The first component needed in the calculation of $P_A\text{O}_2$ is the $P_a\text{CO}_2$. This variable can be measured directly from arterial blood. Alternatively, $P_a\text{CO}_2$ can be approximated from alveolar or expired CO₂ in the absence of significant lung disease.
- The next element needed to calculate $P_A\text{O}_2$ is the $P_I\text{O}_2$. $P_I\text{O}_2$ is the partial pressure of inspired oxygen and can be calculated using the following formula:

$$P_I\text{O}_2 = \text{FiO}_2 * (P_B - P_{\text{H}_2\text{O}})$$

- $P_I\text{O}_2$ incorporates both barometric pressure (P_B) and water vapor pressure ($P_{\text{H}_2\text{O}}$) based on the universal gas law which relates the partial pressures of a combination of gases to their volumes and temperatures. At sea level, P_B is 760 mmHg, and P_B falls as altitude increases. $P_{\text{H}_2\text{O}}$ must also be considered since inspired gas is warmed and saturated as it moves through the respiratory system. At a normal body temperature of 37 °C, $P_{\text{H}_2\text{O}}$ is 47 mmHg. Therefore, for inspired room air gas with an FiO_2 of 0.21 at sea level, the $P_I\text{O}_2 = 0.21 * (760 - 47) = 150$ mmHg.
- The final component of the alveolar gas equation is the respiratory quotient (R). The respiratory quotient is the ratio of CO₂ elimination to O₂ consumption, but direct measurement of these two variables is often difficult and impractical in the clinical setting, especially in pediatric and neonatal patients. In most circumstances, R can be estimated to be 0.8, but some variability does exist depending on the dietary balance of carbohydrates, protein, and fat.

Bedside calculation of $P_A\text{O}_2$ is easily performed using the alveolar gas equation. This calculation provides important clinical data since $P_A\text{O}_2$ can be used to determine the alveolar-arterial oxygen gradient ($P_A\text{O}_2 - P_a\text{O}_2$). This difference between oxygenation at the alveolar level versus that measured in arterial blood allows one to assess for adequacy of tissue oxygenation. Normally, a gradient of 5–15 mmHg exists between the partial pressure of oxygen in the alveolus and arterial blood, but this gradient may increase substantially in a number of pathophysiologic states (Table 3.1).

The P_{AO_2} calculation provides an important global measure of alveolar oxygenation, but considerable differences in ventilation exist in different regions of the lung. As one travels from the apex of the lung to the base, ventilation per unit of volume increases (Fig. 3.1). This increase in ventilation is largely related to the effects of gravity, which create higher (or less negative, in the spontaneously breathing patient) intrapleural pressures at the base of the lung relative to the apex. In the supine patient, this difference disappears, and a posterior-anterior gradient is produced with more ventilation per unit of lung volume in the posterior (dependent) portion of the lung. This ventilation gradient, coupled with regional blood flow differences within the lung, has important therapeutic implications and can significantly impact mechanical ventilation strategies for a variety of pathophysiologic states (Radford 1955).

Table 3.1 Causes of hypoxemia

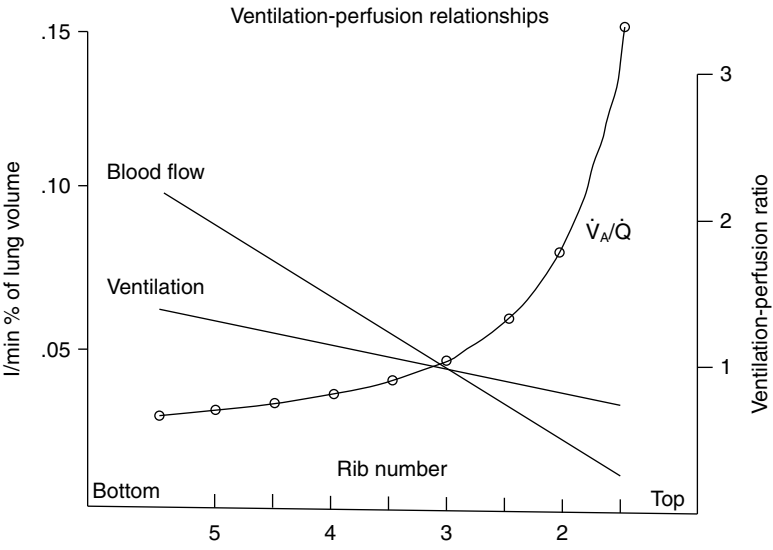
1. Low FiO_2
2. Hypoventilation
3. Ventilation-perfusion mismatch
4. Impaired alveolar-capillary interface diffusion
5. Intrapulmonary shunt
6. Pulmonary artery desaturation
7. Hemoglobinopathies

3.3 Intrapulmonary Shunt

V/Q matching is an important element in pulmonary gas exchange since only the gas that reaches the alveolar-capillary interface is available for exchange. Under ideal circumstances, pulmonary perfusion (Q) would perfectly match the differential ventilation (V) of various lung units and create a ventilation to perfusion ratio (V/Q ratio) of 1. As discussed previously, regional differences exist within the lung, and ventilation is higher in dependent lung units. Similarly, pulmonary perfusion is higher in dependent regions of the lung, but there is a greater change in perfusion across the lung when compared to ventilation. This higher rate of increase in perfusion from nondependent to dependent lung regions leads to imperfect V/Q matching. The different gradients between ventilation and perfusion across the lung lead to a high V/Q ratio (>1) in the nondependent regions and a low V/Q ratio (<1) in the dependent regions (Fig. 3.1). Under normal circumstances, global ventilation is well matched to global perfusion, producing an overall pulmonary V/Q ratio of approximately 0.8.

A small percentage of pulmonary blood flow in the healthy lung travels through non-ventilated portions of the lung, providing an extreme example of V/Q mismatching. This blood represents the intrapulmonary shunt and is sometimes referred to as venous admixture. Some degree of

Fig. 3.1 Distribution of ventilation and blood flow and change in ventilation-perfusion ratio down the upright lung (Excerpted from West (2005b))



intrapulmonary shunting is normal, and the shunt fraction is defined as the percentage of pulmonary blood flow traveling through non-ventilated lung regions. The normal shunt fraction is less than 5 % and is usually closer to 1–2 % of total pulmonary blood flow (or cardiac output) (Cruz and Metting 1987; West 2005b). Within the normal lung, intrapulmonary shunt is caused by three main factors: (1) desaturated bronchial arterial blood that returns directly to the pulmonary veins after O_2 delivery to the bronchi, (2) Thebesian veins which return blood directly to the left ventricle after perfusing the myocardium, and (3) alveolar collapse in the bases or most dependent regions of the lung. These portions of the lung are perfused but unable to be ventilated due to the alveolar collapse, thus, creating a V/Q ratio of 0.

The intrapulmonary shunt fraction can be estimated using the following formula:

$$Q_s / Q_t = \frac{C_c O_2 - C_a O_2}{C_c O_2 - C_v O_2}$$

where:

Q_s =shunted fraction of cardiac output (intrapulmonary shunt)

Q_t =total cardiac output

$C_c O_2$ =oxygen content of end pulmonary capillary blood

$C_a O_2$ =oxygen content of arterial blood (systemic)

$C_v O_2$ =oxygen content of venous blood (pulmonary artery)

Clinically, this formula can provide information regarding the adequacy of gas exchange and the magnitude of intrapulmonary shunt as a potential contributor to inadequate oxygenation. Determining the degree of intrapulmonary shunt may assist in the evaluation of therapeutic options and mechanical ventilation strategies (Cruz and Metting 1987; Fink et al. 2005; Furchman and Zimmerman 2006; Marino 1998). When using this formula clinically to calculate the shunt fraction, a few assumptions are usually involved. When calculating $C_c O_2$, the oxygen saturation of hemoglobin (SaO_2) is generally assumed to be 100 % due to the fact that in the vast majority of circumstances, blood is fully saturated after traversing the pulmonary capillary. It must be noted that this assumption may not be true in the presence of lung

pathology. Furthermore, pulmonary artery catheters are not available in most situations, and mixed venous ($SmvO_2$) or central venous ($ScvO_2$) oxygen saturations can provide a reasonable estimation of hemoglobin saturation in blood returning to the heart for $C_v O_2$ calculations. Lastly, all units for oxygen content should be in mL O_2 /dL blood.

While a small degree of intrapulmonary shunting is normal, there are a number of circumstances in which the shunt fraction may be significantly increased, thus, worsening V/Q mismatch. These pathophysiologic states may lead to regional changes in the lung that impact either pulmonary perfusion, ventilation, or both. This increased intrapulmonary shunt and worsening V/Q mismatch have significant detrimental effects on gas exchange and systemic oxygenation.

Hypoxemia secondary to an intrapulmonary shunt normally does not respond to supplemental oxygen. Increased FiO_2 is ineffective in this circumstance because the shunted blood traveling through capillaries adjacent to non-ventilated lung units is not exposed to the increased alveolar oxygen concentrations. Shunted blood remains desaturated and mixes with fully saturated blood as it returns to the pulmonary veins, causing a less than expected response to oxygen administration (Fig. 3.2).

Increasing the shunt fraction does not usually influence CO_2 elimination. Transient increases in the concentration of CO_2 in shunted blood lead to

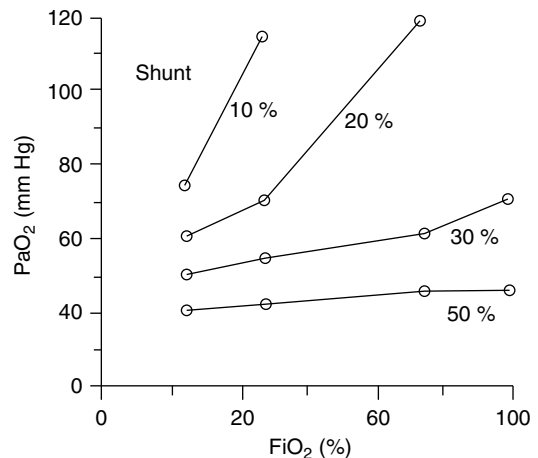


Fig. 3.2 Response to increasing FiO_2 with variation in intrapulmonary shunt fraction (Excerpted from Fink et al. (2005))

an increased ventilatory drive to increase minute ventilation and maintain a normal $P_a\text{CO}_2$.

3.4 Dead Space

As previously discussed, a certain quantity of dead space exists in healthy lungs due to the portion of inspired gas that remains in the conducting airways and is unavailable for gas exchange. In direct contrast to intrapulmonary shunting, dead-space ventilation represents “wasted” ventilation to areas of the lung that are poorly perfused, or not perfused at all. In these lung units, the V/Q ratio approaches infinity as perfusion (Q) approaches zero. Anatomic dead space is a fixed volume for a given individual and historically has been estimated as 1 mL/lb (0.45 mL/kg) of body weight (Nunn et al. 1959; Numa and Newth 1996; Furchman and Zimmerman 2006; Fink et al. 2005). Most clinicians feel that this estimate is reasonable, but there are recent data that dispute the accuracy of this approximation (Brewer et al. 2008).

In the absence of lung disease, dead space is composed almost entirely of air that remains in the nasopharynx and conducting airways (anatomic dead space), and there is essentially no alveolar contribution. When lung pathology is present, additional alveolar dead space develops. Alveolar dead space is commonly caused by overdistension of healthy lung units during mechanical ventilation. Other potential causes of alveolar dead space include destruction of the alveolar-capillary membrane, poor cardiac output, and pulmonary vascular obstruction. It should be stressed that alveolar dead space is negligible in the absence of lung disease and anatomic dead space predominates. However, depending on the degree of lung injury, alveolar dead space may be of much greater consequence. Overall, total physiologic dead-space ventilation (anatomic plus alveolar dead space) is described as a ratio to total ventilation and expressed as

$$V_D / V_T$$

where V_D is the total volume of dead-space ventilation (including both anatomic and alveolar dead space) and V_T is the total inspired volume

for a given breath. The V_D/V_T ratio can be estimated at the bedside using the following modification of the Bohr equation:

$$V_D / V_T = \frac{P_a\text{CO}_2 - P_E\text{CO}_2}{P_a\text{CO}_2}$$

where $P_a\text{CO}_2$ is the arterial partial pressure of CO_2 and $P_E\text{CO}_2$ is the mixed expired concentration of CO_2 .

In healthy adults, dead-space ventilation is approximately 20–30 % of total ventilation, yielding a V_D/V_T of 0.2–0.3. However, pediatric and neonatal patients may have a larger percentage of dead space due to anatomical differences in head and body size, with normal ratios for V_D/V_T as high as 0.4–0.5 having been reported. In the setting of lung pathology, V_D/V_T may approach 1, and this change is predominantly due to increases in the degree of alveolar dead space. V_D/V_T has important therapeutic implications, and clinicians can quickly estimate this ratio at the bedside using easily available data. Not only can the V_D/V_T ratio be followed as an indicator of the degree of lung injury, but it also may be an important tool in the development of an effective ventilator strategy to optimize V/Q matching.

3.5 Blood-Gas Equilibrium

Adequate matching of ventilation and perfusion depends on diffusion across the interface created at the alveolar-capillary junction. The transfer of both O_2 and CO_2 is driven by simple diffusion across the alveolar-capillary membrane. As with any gas, this diffusion is governed by Fick’s law (West 2005a, Fink et al. 2005, Furchman and Zimmerman 2006, Marino 1998). The Fick principle states that the rate of gas exchange via passive diffusion depends on properties of both the membrane and the gases involved. Gas transfer rates are directly proportional to the surface area and inversely proportional to the thickness of the membrane. In addition, the solubility coefficient of the gases (which depends on both the intrinsic solubility and the molecular weight of the gas) and the difference between the partial pressures of the gases on opposite sides of the membrane

directly contribute to rates of gas transfer. Fick's relationship between these factors can be represented by the following formula:

$$\text{Diffusion Rate} = \frac{K * A * (P_1 - P_2)}{t}$$

where K is the solubility coefficient (constant) for a given gas, A is the surface area involved in gas exchange, $P_1 - P_2$ is the difference between partial pressures across the membrane for a given gas, and t is the thickness of the membrane (distance for diffusion).

The structure of the alveolar-capillary interface in the lung is well suited for remarkably efficient gas exchange. Under normal circumstances, there are approximately 75 m² of alveolar surface area available for gas exchange in the lung. The membrane separating the pulmonary capillaries and alveoli is in the range of 0.3 μm in many places, creating an ideal situation for diffusion. These membrane properties lead to exceptional gas exchange, and it is the rare circumstance that the structure of the alveolar-capillary membrane causes diffusion limitations (Slonim and Pollack 2006; Motoyama and Davis 2006).

Due to these favorable membrane characteristics, most gases are perfusion limited, meaning that their rate of diffusion depends entirely on the amount of available blood passing by the membrane. On average, an individual RBC spends approximately 0.7–0.8 s within the alveolar capillary of the lung. This brief time is approximately three times that which is necessary for complete equilibration of both oxygen and carbon dioxide across the alveolar-capillary interface. Complete transfer of O₂ across the membrane usually occurs within 0.25 s, and CO₂ equilibrates approximately 20 times faster than O₂. This rapid transfer is driven primarily by the large partial pressure gradients that exist between the alveolus and the pulmonary capillary (West 2005b; Slonim and Pollack 2006; Motoyama and Davis 2006).

As blood enters the pulmonary capillary, the P_{aO_2} is approximately one third of the P_{AO_2} , creating a large gradient to drive gas transfer from the alveolus into the RBC. Normally, diffusion of O₂ is complete long before RBCs reach the end of the pulmonary capillary. However, there are two

circumstances in which oxygen may become diffusion limited, even in the absence of lung pathology. One situation in which diffusion limitation may occur is when well-trained athletes vigorously exercise. The significant increase in cardiac output that may occur in this setting leads to increased pulmonary blood flow and faster RBC transit time through the pulmonary capillaries. Transit time within the lungs can approach the 0.25 s necessary for oxygen equilibration and can potentially become a limiting factor for diffusion. A second situation in which oxygen may become diffusion limited occurs with substantial decreases in P_{AO_2} , as may be seen at high altitudes. The mechanism for this limitation is a slower rate O₂ transfer due to the decreased partial pressure gradient across the alveolar-capillary membrane.

Diffusion limitation may also occur due to the intrinsic properties of certain gases. Carbon monoxide (CO) is diffusion limited because of its strong affinity for hemoglobin. As CO diffuses across the alveolar-capillary membrane, it rapidly binds to hemoglobin within the RBC, creating little change in the partial pressure of CO. This minimal change in downstream partial pressure leads to a persistently large partial pressure gradient across the membrane. Since diffusion is largely driven by this gradient, CO continues to diffuse at a high rate during the entire transit time of the RBC through the pulmonary capillary. CO is one of the few inhaled gases that is diffusion limited in this fashion.

As discussed above, gas equilibration is either limited by perfusion or diffusion in the healthy lung. There are also circumstances in which the structural integrity of the alveolar-capillary membrane may be altered, leading to further limitation of gas exchange. Loss of surface area for gas exchange due to direct lung injury from a variety of causes can lead to impaired gas exchange. Similarly, any increase in thickness of the alveolar-capillary interface can also impair diffusion of gases. There are a number of pathophysiologic processes in the lung that can substantially impair gas exchange by disrupting the blood-gas equilibrium which include parenchymal lung disease, pulmonary edema, interstitial lung disease, pulmonary fibrosis, or impaired cardiac output.

3.6 Tissue Oxygenation

Ultimately, the oxygen that diffuses across the alveolar-capillary membrane must be delivered to the tissues to meet the metabolic demands of the body. Tissue oxygenation is dependent on both cardiac output and the amount of oxygen transported in the bloodstream (i.e., arterial oxygen content). Most oxygen transport occurs within the RBCs via binding with hemoglobin (Hgb) (Edwards et al. 1993). Hemoglobin is a complex molecule composed of four polypeptide chains, each of which has a central heme ring. These polypeptide chains occur in varying combinations depending on their amino acid sequences (i.e., alpha, beta, gamma) with the variants each having differing affinities for oxygen binding.

The heme protein of hemoglobin contains iron and can bind O₂ only in its ferrous (Fe²⁺) form. The adequacy of oxygen transport from the alveolus to the tissue level depends primarily on this oxygen-hemoglobin relationship, which is graphically represented by the oxygen-hemoglobin dissociation curve (Fig. 3.3).

The shape of the oxygen-hemoglobin dissociation curve is determined by the interaction among the four heme proteins of the Hgb molecule. As oxygen binds to one of the heme moieties, binding affinity to subsequent heme subunits is increased, creating a sigmoidal rela-

Table 3.2 Factors affecting the oxyhemoglobin dissociation curve

1. pH
2. P _a CO ₂
3. Temperature
4. 2,3-DPG (diphosphoglycerate)
5. Hemoglobin polypeptide subunit composition

tionship. This nonlinear, sigmoidal relationship is crucial for oxygen loading at the alveolar-capillary interface and unloading at the tissue level. Under normal circumstances, Hgb saturation is maintained in the range of 97–100 % at any P_aO₂ greater than approximately 70 mmHg. There are two other notable points on the oxygen-hemoglobin dissociation curve. First, as P_aO₂ falls to approximately 40 mmHg, hemoglobin saturation drops quickly to 75 % due to the steep slope of the oxygen-hemoglobin dissociation curve. This point (P_aO₂ of 40 mmHg with a SaO₂ of 75 %) represents the usual composition of mixed venous blood as it returns to the heart. A second important point on the oxygen-hemoglobin dissociation curve is the point at which the hemoglobin saturation is 50 % (P₅₀). The P₅₀ usually occurs at a P_aO₂ of 26 mmHg.

The P₅₀ is the reference point often used to discuss shifts in the oxygen-hemoglobin dissociation curve. These shifts may occur due to changes in a number of physiologic variables (Table 3.2). Rightward shift of the oxygen-hemoglobin dissociation curve represents an increase in P₅₀ and a decreased O₂ binding affinity for Hgb (lower Hgb saturation) for any given P_aO₂. The rightward-shifted oxygen-hemoglobin dissociation curve facilitates oxygen delivery and release. Decreases in pH and increases in P_aCO₂ shift the oxygen-hemoglobin dissociation curve to the right via the *Bohr effect*. Increased temperature also shifts the oxygen-hemoglobin dissociation curve to the right, further facilitating release of oxygen. The rightward shift of the oxygen-hemoglobin dissociation curve represents a compensatory response to improve oxygen unloading in the setting of acidemia or hyperthermia.

2,3-DPG is a highly charged metabolic by-product found in RBCs. 2,3-DPG binds deoxygenated hemoglobin and reduces subsequent oxygen

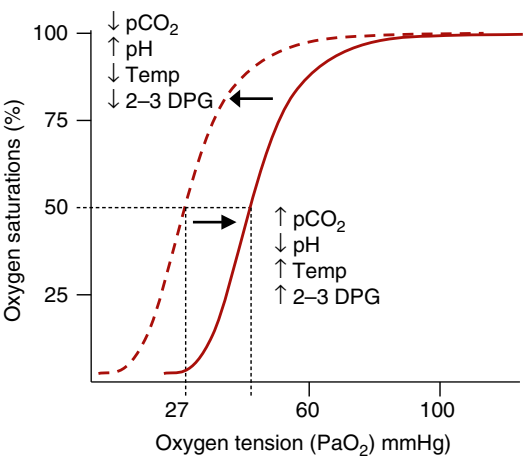


Fig. 3.3 Oxygen-hemoglobin dissociation curve (Excerpted from West (2005a))

binding affinity, promoting release of oxygen. An increased level of 2,3-diphosphoglycerate (DPG) shifts the oxygen-hemoglobin dissociation curve to the right.

Conversely, leftward shift of the oxygen-hemoglobin dissociation curve represents an increase in O₂ binding affinity for hemoglobin at any given P_aO₂, favoring oxygen loading and uptake. Increased pH, decreased P_aCO₂, decreased temperature, and decreased levels of 2,3-DPG shift the oxygen-hemoglobin dissociation curve to the left and augment oxygen uptake.

The structure of Hgb also can impact the oxygen-hemoglobin dissociation curve. One example of the influence of Hgb structure on oxygen binding affinity occurs in the fetus. In the fetus, a leftward-shifted oxygen-hemoglobin dissociation curve is seen due to the presence of fetal hemoglobin. Fetal hemoglobin contains two gamma chains instead of the beta chains present in normal adult Hgb, which causes an increased affinity for oxygen. These gamma chains have a diminished interaction with 2,3-DPG when compared to adult hemoglobin, shifting the oxygen-hemoglobin dissociation curve to the left. Similarly, hemoglobinopathies are another group of conditions in which the presence of abnormal hemoglobin molecules impact oxygen binding and the location of the oxygen-hemoglobin dissociation curve.

Hgb is the primary determinant of oxygen content in the blood, and the overall content of oxygen in arterial blood (C_aO₂) can be determined using the following formula:

$$C_aO_2 = 1.39 * [SaO_2 * Hgb] + 0.003 * P_aO_2$$

where:

C_aO₂ (vol % or mL O₂/100 mL blood) = oxygen content of arterial blood

SaO₂ (%) = oxygen saturation of hemoglobin

Hgb (g/dL) = hemoglobin level

P_aO₂ (mmHg) = arterial partial pressure of oxygen

0.003 mL O₂/dL blood = constant based on Henry's law relating the volume of a dissolved gas and the partial pressure of that gas

1.39 mL O₂ = the amount of oxygen bound by one gram of hemoglobin (may be estimated as 1.32–1.39 mL O₂ depending on calculation methods)

C_aO₂ is one of the primary determinants of oxygen delivery (DO₂) to the tissues. DO₂ is the product of C_aO₂ and cardiac output (CO) and can be represented by the following formula:

$$DO_2 \text{ (mLO}_2 \text{ / min)} = C_aO_2 \text{ (mLO}_2 \text{ / dL blood)} * CO \text{ (L / min)} * 100$$

In the normal state, DO₂ is approximately four times the amount of O₂ required by the tissues. This excess oxygen delivery allows the body to compensate for wide variations in DO₂ without compromising tissue metabolism and homeostasis.

3.7 Metabolic Rate

Metabolic needs of the tissues are quantified as oxygen consumption (VO₂). VO₂ is the rate of oxygen uptake and utilization by the tissues and can be calculated using a modification of the Fick equation:

$$VO_2 \text{ (mLO}_2 \text{ / min)} = DO_2 \text{ (mLO}_2 \text{ / min)} * [SaO_2 \text{ (\%)} - SvO_2 \text{ (\%)}]$$

where:

VO₂ = oxygen consumption

DO₂ = oxygen delivery

SaO₂ = oxygen saturation of hemoglobin in arterial blood

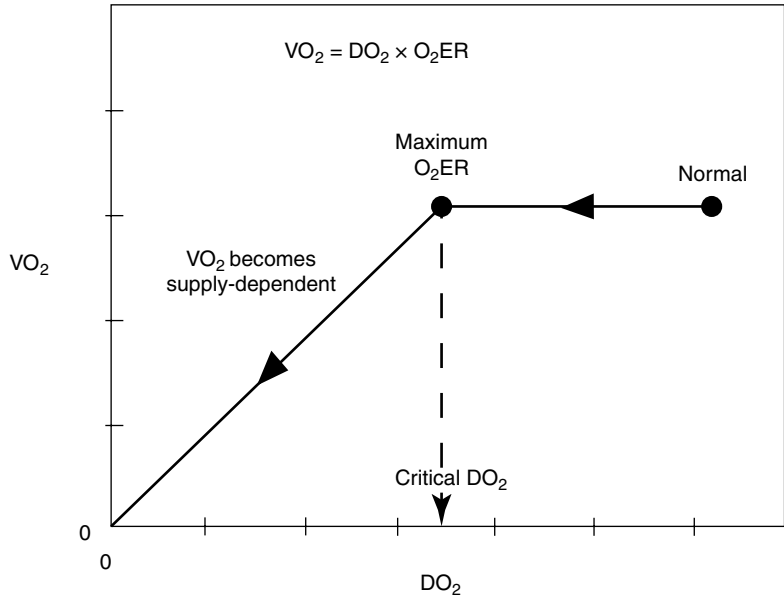
¹SvO₂ = oxygen saturation of hemoglobin in venous blood

(SaO₂ – SvO₂) = oxygen extraction by the tissues

Under normal circumstances, DO₂ is approximately four times VO₂. When SaO₂ is 99–100 %, this relationship leads to a SvO₂ (or SmvO₂) of approximately 75 %, and an overall oxygen extraction (SaO₂ – SvO₂) of approximately 25 % (West 2005a; Leach and Treacher 1994; Leach and Treacher 2002). As DO₂ falls, the body compensates by increasing the extraction of oxygen at the tissue level. This increase in oxygen extraction causes SvO₂ (or SmvO₂) to fall. In general, the tissues and organs of the body receive an excess supply of oxygen, and, thus, an increased

¹Ideally, SvO₂ for these calculations is a sample of mixed venous blood and reflects SmvO₂.

Fig. 3.4 DO_2/VO_2 relationship (Excerpted from Marino (1998))



oxygen extraction does not limit VO_2 over a wide range of DO_2 (Fig. 3.4).

In healthy patients, VO_2 is generally independent of DO_2 . However, there are a number of pathophysiologic states in which impairment of gas exchange, transport, or utilization may cause DO_2 to fall below a critical point (Fig. 3.4). At this point, VO_2 becomes dependent on oxygen delivery (Morisaki and Sibbald 2004). This “oxygen supply dependency” is a pathologic state that may be seen in critical illness in which a linear relationship exists between VO_2 and DO_2 . Under these circumstances, any intervention that improves DO_2 will subsequently increase VO_2 in a linear fashion and improve tissue homeostasis. This relationship provides the physiologic basis for many goal-directed therapies that are routinely implemented in the ICU (Shoemaker et al. 1973; Shoemaker et al. 1988; Taylor et al. 1991; Appel and Shoemaker 1992; Gattinoni et al. 1995).

3.8 Interpretation of Arterial and Venous Blood Gases

The relationship between DO_2 and VO_2 can be affected by the adequacy of pulmonary gas exchange. While there are a number of noninvasive measurements for the assessment of gas

Table 3.3 Normal arterial blood gas values (room air)

pH	7.35–7.45
pCO_2	35–45 mmHg
P_aO_2	85–110 mmHg
HCO_3	22–24 mmol/L
Base excess	0
SAO_2	95–100 %

exchange, arterial blood gas (ABG) measurement is an important element in the evaluation of oxygenation, carbon dioxide elimination, and metabolic state. ABGs are immediately available in the ICU and are the most common test ordered by ICU providers (Muakkassa et al. 1990). Interpretation of blood gases is a crucial skill for all who care for critically ill patients.

ABG analysis involves the direct measurement of pH, P_aCO_2 , and P_aO_2 . SAO_2 is either calculated based on standard oxygen-hemoglobin dissociation curves or measured directly by co-oximetry. Bicarbonate (HCO_3) is determined by the balance between hydrogen ions and partial pressure of CO_2 in the blood. Base excess is usually reported as a part of ABG results, and this value reflects the body’s metabolic state irrespective of the gas exchange variables. There is a relatively narrow range of normal values for ABG results (Table 3.3), but these measurements may be impacted by equipment, collection technique, temperature, and a number of other metabolic factors.

Table 3.4 Expected changes in arterial blood gases with acid-base disturbances

Acid-base abnormality	Primary change	Secondary compensation
Respiratory acidosis	$\text{PCO}_2 \uparrow$	$\text{HCO}_3 \uparrow$
Respiratory alkalosis	$\text{PCO}_2 \downarrow$	$\text{HCO}_3 \downarrow$
Metabolic acidosis	$\text{HCO}_3 \downarrow$	$\text{PCO}_2 \downarrow$
Metabolic alkalosis	$\text{HCO}_3 \uparrow$	$\text{PCO}_2 \uparrow$

Interpretation of an ABG begins with determination of the primary abnormality in gas exchange. In most circumstances, the pH is a reflection of the primary underlying disturbance. Elevation of pH reflects a primary alkalosis, and low pH indicates acidosis as the primary process. Once the primary abnormality is established, the additional ABG values should be used to determine whether the underlying disturbance is respiratory or metabolic in nature (Table 3.4). For metabolic derangements, the anion gap obtained from basic chemistry values is an important adjunct in establishing an etiology. The normal anion gap is less than 12 and can be calculated using the following formula:

$$\text{Anion Gap} = \text{Na} - (\text{Cl} + \text{HCO}_3)$$

where Na and Cl are the serum concentrations of sodium and chloride, respectively.

ABGs also reflect the body's compensatory response as it attempts to maintain a normal pH in the face of acid-base abnormalities (Table 3.4). When a primary metabolic disturbance is present (either acidosis or alkalosis), the response of the lungs is relatively immediate as minute ventilation is adjusted to correct pH. However, the renal response required to compensate for primary respiratory acid-base derangements requires 24–48 h to achieve steady state as the proximal tubules of the kidneys alter HCO_3 reabsorption.

These compensatory responses occur in a predictable fashion based on the relationship between $P_a\text{CO}_2$ and HCO_3 in the blood. Given the time course involved in the renal response to respiratory abnormalities, the magnitude of expected compensatory change varies with the

Table 3.5 Calculation of expected compensatory response with acid-base disturbances

Primary process	Anticipated change
Acute respiratory acidosis	$\text{pH change} = 0.008 * (\text{PCO}_2 - 40)$
Acute respiratory alkalosis	$\text{pH change} = 0.008 * (40 - \text{PCO}_2)$
Chronic respiratory acidosis	$\text{pH change} = 0.003 * (\text{PCO}_2 - 40)$
Chronic respiratory alkalosis	$\text{pH change} = 0.017 * (40 - \text{PCO}_2)$
Metabolic acidosis	$\text{PCO}_2 \text{ change} = 1.5 * \text{HCO}_3 + 8$
Metabolic alkalosis	$\text{PCO}_2 \text{ change} = 0.7 * \text{HCO}_3 + 21$

acuity of the process. These anticipated changes can be easily calculated (Table 3.5). These calculations are especially important in the context of mixed acid-base disturbances caused by more than one underlying process.

ABGs provide important data regarding the adequacy of gas exchange at both the pulmonary and tissue level, but there are circumstances in which analysis of the venous blood gas (VBG) may also provide helpful additional information. When drawn from the superior vena cava/right atrial (SVC/RA) junction, the VBG represents a sample of mixed venous blood. As discussed previously, the saturation of mixed venous blood (SmvO_2) is an important marker for the balance between oxygen uptake and delivery and is used in a number of clinically important calculations including oxygen delivery, oxygen consumption, Q_p/Q_s , and the intrapulmonary shunt fraction.

SmvO_2 and VBG results are often helpful in the assessment of global gas exchange, but VBG interpretation must be undertaken with caution when the site of sampling is not mixed venous in origin. The pH of venous blood drawn from any site provides a reasonable estimate of acidemia, but substantial differences may exist in the partial pressures of oxygen and carbon dioxide at the local level. These partial pressures may not reliably demonstrate adequacy of oxygenation or ventilation given the variation in oxygen utilization and metabolism by different tissues and organs. VBGs do often provide important adjunctive information regarding gas exchange and metabolic state but should not replace the ABG in the assessment of overall acid-base balance and gas exchange.

Essentials to Remember

- The primary goal of pulmonary gas exchange is tissue O₂ delivery and CO₂ elimination.
- Alveolar ventilation and oxygenation are related by the alveolar gas equation: $P_A O_2 = F_i O_2 * (P_B - P_{H_2O}) - P_a CO_2 / R$.
- A gradient for V/Q ratio exists across the lung due to increases in both ventilation and perfusion as one moves from nondependent to dependent regions. In nondependent lung units, the V/Q ratio is high, and in the dependent areas of the lung, the V/Q ratio approaches 0.
- Intrapulmonary shunt represents blood flow through non-ventilated lung units, and the normal shunt fraction is <5 % of cardiac output.
- Dead-space ventilation represents “wasted” ventilation to areas of the lung without blood flow.
- Dead-space ventilation is made up of two components: (1) anatomic dead space, which can be roughly approximated as 1 mL/lb (0.45 mL/kg) of body weight, and (2) alveolar dead space, which can be caused by overdistension secondary to mechanical ventilation.
- Dead-space ventilation is often described as it relates to tidal volume (V_D/V_T). This ratio is an important indicator of the degree of lung injury and can be easily estimated at the bedside.
- O₂ and CO₂ diffuse rapidly across the alveolar-capillary interface, making gas exchange limited by diffusion only in rare circumstances.
- The sigmoidal oxygen-hemoglobin dissociation curve is designed for optimal oxygen loading in the lung and unloading at the tissue level.
- Acidosis, elevated $P_a CO_2$, hyperthermia, and increased 2,3-DPG levels shift the oxygen-hemoglobin dissociation curve to the right and facilitate oxygen unloading. Conversely, alkalosis, low $P_a CO_2$, hypothermia, and decreased

2,3-DPG levels shift the oxygen-hemoglobin dissociation curve to the left and facilitate oxygen loading.

- O₂ content of the blood depends primarily on hemoglobin and oxygen saturation, and dissolved O₂ is a minor contributor to oxygen delivery.
- Oxygen delivery is usually well in excess of oxygen consumption, and VO₂ is stable over a wide range of DO₂ values.
- ABGs can be utilized to analyze both the primary derangement of gas exchange and the adequacy of the body’s compensatory response.

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4.1 Physiology of the Upper Airway and Control in Breathing

Alastair A. Hutchison

Educational Aims

- Describe the expanded concept of breathing in terms of multiple motor functions that ensure airway protection, volume homeostasis, and ventilation.
- Describe the upper airway structures and how their functions affect the entire airway.
- Describe the nasal functions involved in air conditioning, in protection, in the maintenance of airway patency, and in the consequences of nasal bypass and obstruction.
- Describe the oral cavity and pharyngeal regions and control of airway patency.
- Describe factors involved in obstructive sleep apnea and the effects of CPAP therapy.
- Describe the coordination of sucking, nutritive swallowing, and breathing during development and the relationship to apnea and bradycardia.
- Describe the importance of nonnutritive swallowing in pharyngeal clearance and how this may be influenced by CPAP.
- Describe the three major functions of the larynx involving breathing.
- Describe the triple mechanism of laryngeal closure in airway protection.
- Describe how flow and subglottic volume are controlled during eupnea.
- Describe the integrative nature of the central control of laryngeal functions.
- Describe the roles of laryngeal muscles and their coordination with pump muscles during development and in eupnea, sighs, grunting, incremental breathing, and gasping.
- Describe how this information has been/ can be applied in respiratory support.
- Describe afferent inputs that alter laryngeal muscle functions and alter breathing and cardiovascular function.
- Describe the impact of central behavioral state and induced central depression upon laryngeal function and the interactions with detected changes in the gaseous environment.

4.1.1 Introduction: Breathing and the Upper Airway

It is impossible for anyone to find the correct function of a part unless he is perfectly acquainted with the action of the whole instrument. Galen, AD 120–200.

Breathing consists of multiple motor acts whose mechanical effects aim to ensure that the airway is protected, has optimal supra- and subglottic volumes, and provides vital ventilation. The upper airway extends from the nose or mouth to the larynx (Seikel et al. 2005), but its functions, in the context of ventilation, extend to the entire airway. Maintenance of airway volume and ventilation is actively controlled by the centrally coordinated activities of nasal, oral, pharyngeal, and laryngeal upper airway muscles and those of the pump muscles. These act in concert with lower airway smooth muscle. Effective breathing requires that the brain coordinates ventilatory functions with cardiovascular function and with other motor acts, e.g., swallowing, postural changes, and speech. Adaptations in breathing must occur appropriately, rapidly, and constantly. Protective and mechanical changes occur in milliseconds. Changes in circulatory gas transport alter breathing within seconds. Other adjustments optimize breathing in tune with changes in growth, aging, metabolism, and the environment. This chapter addresses how each upper airway structure plays critical roles in the dynamic processes of breathing.

4.1.2 Nasal Functions in Breathing

... we would do well to keep our mouths shut and reflect on the marvelous physiology of the nose. Richard Godfrey 1994

4.1.2.1 Air Conditioning and Vascularity

Normal breathing occurs via the nose (Fig. 4.1). Inspired and expired air is conditioned by the

nasal mucosa, whose surface area and blood supply are such that particles are filtered and temperature and humidity are modified. The nasal vascular system can achieve a 25 °C gradient between the nasal ostia and the nasopharynx (Godfrey 1994), a property that enables air breathing at very different environmental temperatures while maintaining a remarkable constancy of temperature and humidity in the lower airway, thereby optimizing cellular function and ciliary action. Given its vascularity, it is not surprising that the nose is a source of nitric oxide, that trauma to the nasal passages can be induced by nasal continuous positive airway pressure (NCPAP) prongs and other cannulae, and that epistaxis can require hospital admission.

4.1.2.2 Nasal Reflexes and Protection

The nose can sniff out noxious substances and protect the airway from particles by sneezing. It can increase its resistance rapidly, switching on a watery secretion “like a tap” (Godfrey 1994), and can trigger laryngeal closure and reduced ventilatory drive (Editorial 1992). The extreme protective reflex response to nasal irritation is the dive reflex that is typified by apnea with glottic closure, bradycardia, and redistribution of blood flow to the brain, heart, and adrenals (see also Sect. 47.3.1) (de Burgh Daly 1997; Editorial 1992). The dive reflex can be triggered by nasal water, tobacco smoke, or ice applied to the trigeminal area (Angell James and de Burgh Daly 1969; de Burgh Daly 1997). Water entry into the nose is dramatic even for adults who “suffer a sense of impending suffocation and the almost impossibility of voluntarily making an inspiratory effort” (de Burgh Daly 1997). Exaggerated dive reflex responses can cause total upper airway closure and cardiac arrest and have been implicated in accidental and deliberately induced deaths (de Burgh Daly 1997).

4.1.2.3 Nasal Patency and Resistance

Nasal breathing in the newborn and infant is the predominant but not obligatory form of breathing and is related to the high position of the

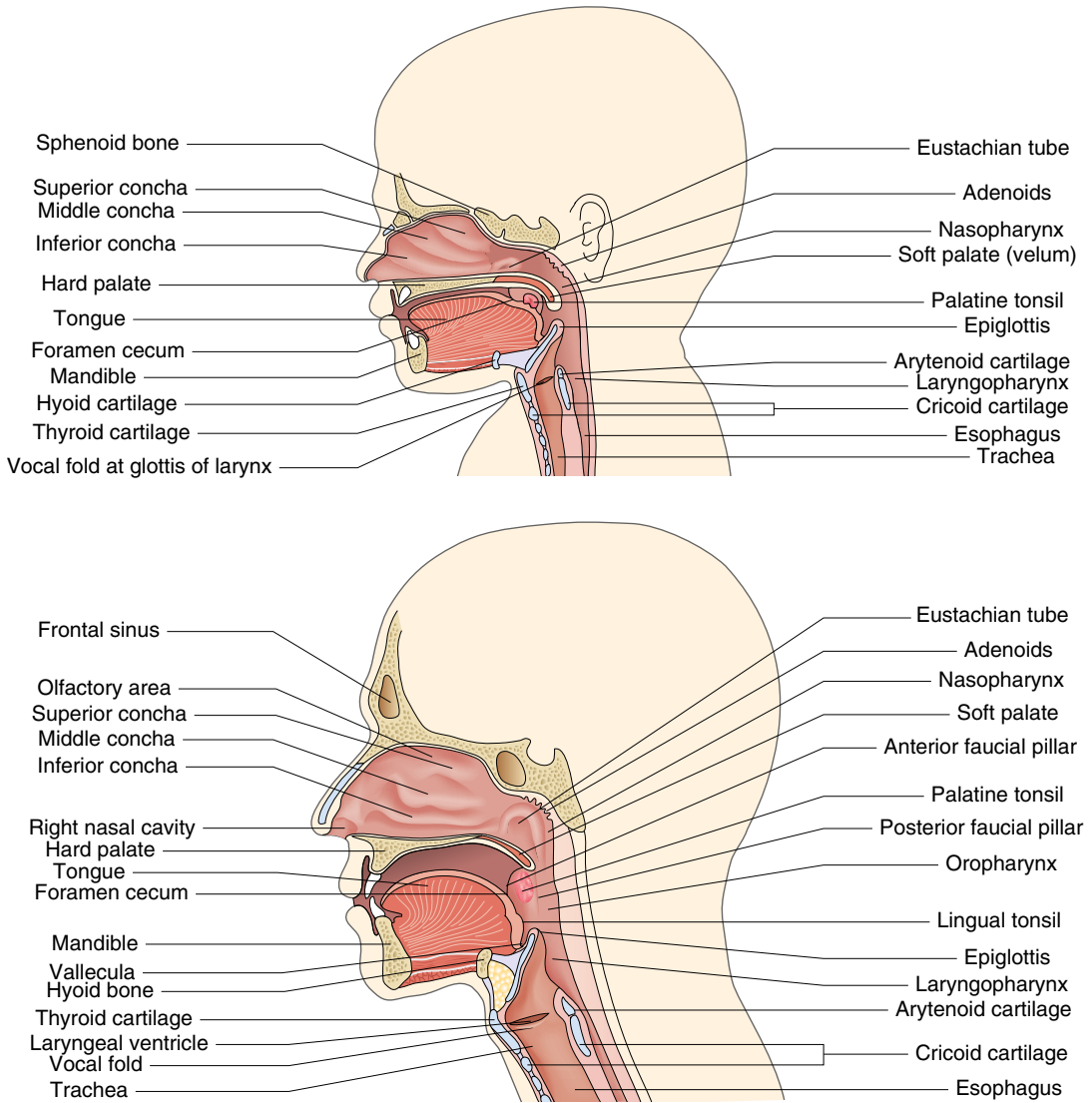


Fig. 4.1 The anatomy of the newborn (*left panel*) and adult (*right panel*) upper airways is shown

epiglottis (Fig. 4.1) (Seikel et al. 2005). There is a nasal cycle whereby resistance alternates from one nostril to the other every 2–4 h in 80 % of humans (Widdicombe 1986). Pressure in the axilla or on the lateral chest increases ipsilateral nasal resistance (Widdicombe 1986). Resistance is highest in the regions adjacent to the external ostia, whose dimensions are altered by the alae

nasi muscles that cause nasal flaring during exercise hyperpnea and respiratory distress, especially in newborns. Newborn nasal resistance exceeds that of the adult in absolute terms but is less than that of their lower airways. Nearly half of the adult's total airway resistance is nasal. Thus, minor increases in nasal resistance can produce major overall effects on breathing (Editorial

1992). In adult humans, nasal occlusion results in a switch to mouth breathing in <5 s (Editorial 1992). Both this switch to oral breathing and the resumption of nasal breathing following release of the occlusion are delayed by nasal and pharyngeal anesthesia. Occlusion of the nasal passages in infants results in mouth breathing in ~ 8 s (range <1 – 32 s) (Editorial 1992; Rodenstein 2004). The response is quicker with advancing age but is decreased in rapid eye movement (REM) sleep, more so at 6 weeks than in the newborn period (Editorial 1992). These observations led to a proposal that the response may be related to the sudden infant death syndrome (SIDS) (Editorial 1992). In premature infants, the change to oral breathing results in a sixfold increase in pulmonary resistance, which over time might result in fatigue with hypoventilation (Miller et al. 1987). Oral breathing places an increased burden on the lower airway to modify the temperature and humidity of inspired gas, presumably via changes in lower airway vascularity. Preventing nasal breathing can decrease gas exchange and functional residual capacity (FRC) (Editorial 1992). Postoperative nasal packing in adults can lead to arterial hypoxemia, apnea, and sleep disturbance, with the latter also occurring in normal volunteers after local anesthesia of the nasal passages (Editorial 1992). In newborn lambs, nasal obstruction also affects gas exchange, with hypoxemia, hypercapnia, and acidosis being observed. These effects are aggravated by carotid body denervation. The impact of nasal obstruction diminishes with advancing age (Editorial 1992). Blockage of the nose (choanal stenosis being an extreme example) can cause obstructive sleep apnea (OSA) (Marcus 2000). Human neonates whose nasal resistance is increased by birth trauma or trauma secondary to repeated suctioning breathe orally. They can have cyanotic episodes, stridor, and hypercapnia; these problems disappear with resolution of the nasal injury (Miller et al. 1987).

In summary, the nose provides air conditioning, and its sensory receptors initiate reflexes that alter upper airway patency and mediate

extended ventilatory changes in response to a challenge.

4.1.3 Oral Cavity and Pharyngeal Functions in Breathing

...after relaxing, many sword swallows are able to relax and breathe while swallowing a sword.
From swordswallow.com 2009.

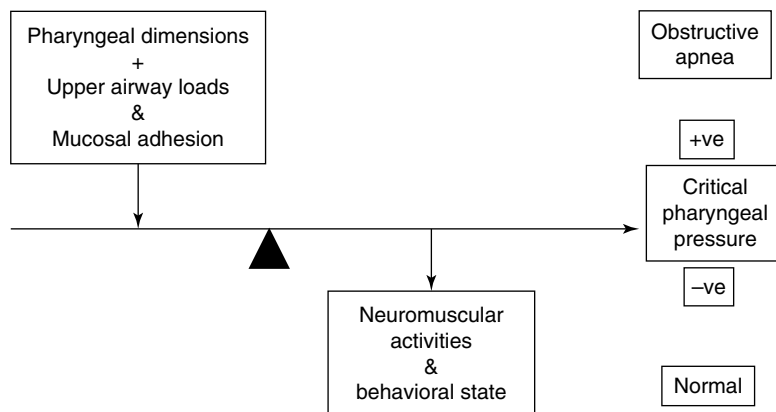
The oral cavity extends from the lips to the plane of the faucial pillars, where it joins the pharynx (Fig. 4.1). The three pharyngeal regions are the nasopharynx, from the posterior nares to the uvula; the oropharynx, from the uvula to the epiglottis; and the laryngopharynx, from the epiglottis to the esophagus. The pharynx is a conduit for air and/or food.

4.1.3.1 Oral Cavity and Pharyngeal Patencies and Obstructive Apnea

The muscles of the tongue, especially the genioglossi, maintain patency of the oral cavity. Pharyngeal patency is a function of the cavity dimensions (Rodenstein 2004) and the balance between the opening forces exerted by pharyngeal muscle activities and the collapsing ones exerted by the tissue–intraparyngeal pressure gradient and by pharyngeal mucosal adhesion (Fig. 4.2). Patency is critically influenced by posture. Narrowing occurs with neck flexion and hyperextension and can alter cavity pressures required to achieve flow. Narrowing can also follow an inspiratory occlusion of the mouth/nose (a load) that augments diaphragmatic activity and thus negative pressure within the pharynx. Upper and lower airway afferents induce reflex compensatory change in glossopharyngeal muscles to offset the load effect (Fig. 4.2) (Bailey and Fregosi 2006).

Obstructive apnea occurs during sleep in ~ 1 – 4 % of children and adults (Marcus 2000). In children, a persistent partial form of upper airway obstruction, obstructive hypoventilation, is

Fig. 4.2 This diagram shows the factors that determine pharyngeal patency – please see text (Modified from Patil et al. (2007))



seen (Marcus 2000). In adults, a spectrum of decreased inspiratory airflow is seen in snoring, upper airway resistance syndrome, and OSA. Pharyngeal OSA occurs when a critical tissue pressure (P_{crit}) exceeds the intrapharyngeal opening pressure (Fig. 4.2) (Marcus 2000; Dempsey et al. 2010) and is influenced by factors that alter pharyngeal dimensions, namely, adenotonsillar hypertrophy, obesity (less common in children than adults), low subglottic airway volume, and craniofacial structural abnormalities. The major role played by the central motor output to the oral cavity and pharyngeal muscles that modify P_{crit} is emphasized by the fact that OSA occurs only in sleep, predominantly in REM sleep in children (Marcus 2000). The following factors also stress the importance of central control in OSA. Obstructive apnea occurring during mixed apnea in preterm newborns involves a direct central mechanism, as shown by the onset of pharyngeal and/or laryngeal closure before diaphragmatic activation (Idiong et al. 1998) (see Sect. 47.3.1). In adults pharyngeal closure can accompany central apnea (Marcus 2000). Central arousal patterns during OSA differ between children and adults (Marcus 2000). Other factors affecting the incidence of OSA are gender, a familial tendency, and racial/ethnic factors (Marcus 2000). Anti-inflammatory medications can benefit OSA, suggesting a role for inflammation in its etiology (Praud and Dorion 2008). Therapy with NCPAP improves OSA by increas-

ing intrapharyngeal pressure and its transverse diameter (Rodenstein 2004), by augmenting lower airway volume and probably by stimulating breathing via pharyngeal pressure sensors (Angell James and de Burgh Daly 1969). In children and adults with OSA, CPAP therapy can improve their metabolism.

4.1.3.2 Sucking, Nutritive Swallowing, and Breathing

The abilities to suck, swallow, and breathe are developed during fetal life (Harding 1986). At all ages, swallowing is accompanied by laryngeal closure. Term newborns and infants up to 12–18 months of age can lock the larynx into the nasopharynx (Figs. 4.1 and 4.3). This separation of the nasopharyngeal–laryngeal air passage from the oropharyngeal nutritive passage enables the term infant to breathe and feed simultaneously but with decreased ventilatory drive. This ability is not developed in the preterm neonate whose sucking pattern is also immature (Lau 2006). Coordination of sucking–swallowing–breathing is defined by the ability to feed “by mouth with no overt signs of aspiration, oxygen desaturation, apnea, or bradycardia” and when “a ratio of 1:1:1 or 2:2:1 suck: swallow: breathe” is attained (Lau 2006). Safe swallowing occurs at end-expiration and end-inspiration (Lau 2006). In term newborns, 55 % of swallows occur at these points of the breathing cycle. In preterm infants, 55 % of swallows occur during deglutition apnea (Lau 2006).

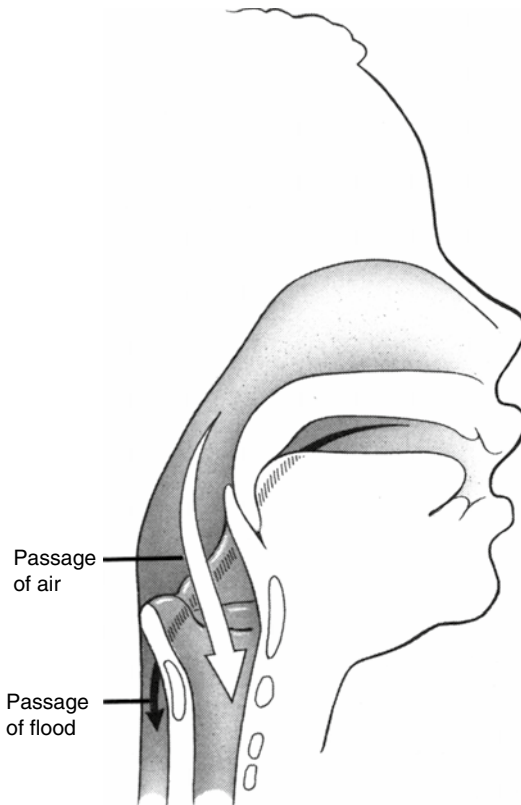


Fig. 4.3 The high position of the infantile larynx allows the epiglottis and uvula to lock, separating the nasopharyngeal-laryngeal air passage from the oropharyngeal nutritive one (From O'Connor, D. Reproduced with permission from Myer et al. (1995). Redrawn by agreement with Springer-Verlag)

4.1.3.3 Nonnutritive Swallowing, Aspiration, and Swallow Breaths

Nonnutritive swallowing (NNS) is “essential for survival,” since >2 L of oral and nasal secretions are produced daily. Without NNS, “the lungs rapidly fill with these secretions, producing death within a few days” (Thach 2005). When pharyngeal secretions reach a critical volume, neural receptors, in the interarytenoid notch, stimulate the laryngochemoreflex which triggers NNS (Thach 2005). The critical pharyngeal volume for NNS may be increased by applied positive pharyngeal pressure, providing an explanation for the decrease in NNS frequency with CPAP (Thach 2005). In adult humans NNS occurs mainly during expiration. In infants NNS

occurs at any time in the respiratory cycle (Thach 2005). Volitional swallowing in adults clears the pharynx and reduces the protective laryngeal adductor reflex. During sleep, the protection provided by NNS and glottic closure is imperfect, and some aspiration is common in normal individuals (Thach 2005). Swallow breaths are short inspirations that precede a swallow, occurring when the upper pharyngeal sphincters are closed (Thach 2005). These breaths are thought to result in pharyngeal air being inhaled as opposed to being swallowed (Thach 2005). The increased gastric air found when positive pharyngeal pressure is applied suggests that CPAP can alter normal pharyngeal clearance mechanisms and infers the need to titrate the applied pressure carefully (Thach 2005). Finally, swallowing may be related to sleep apnea and be part of recovery from sleep apnea (see Sect. 47.3.1) (Thach 2005).

In summary, patency of the oral cavity and the pharynx and the coordination with swallowing and sucking are critical for breathing. The term, but not preterm, newborn can suck and breathe simultaneously, although ventilatory drive is decreased. Physiological control of breathing and swallowing involves important sensory input that limits aspiration and protects the lower airway. Intensive care therapies can alter normal protective, breathing and swallowing functions.

4.1.4 Laryngeal Functions in Breathing and Control in Breathing

Like a Swiss watch, ...our vocal tract depends on the precise functioning of many structures and muscles.” Jared Diamond, 1992 (The Third Chimpanzee).

The larynx has three major functions involving breathing. It serves as a protective structure guarding the subglottic airway; as a flow controller of subglottic absolute and tidal volumes during eupnea and complex coordinated movements; and as a vibratory modulator of flow that generates speech, song, and laughter (Fig. 4.4).

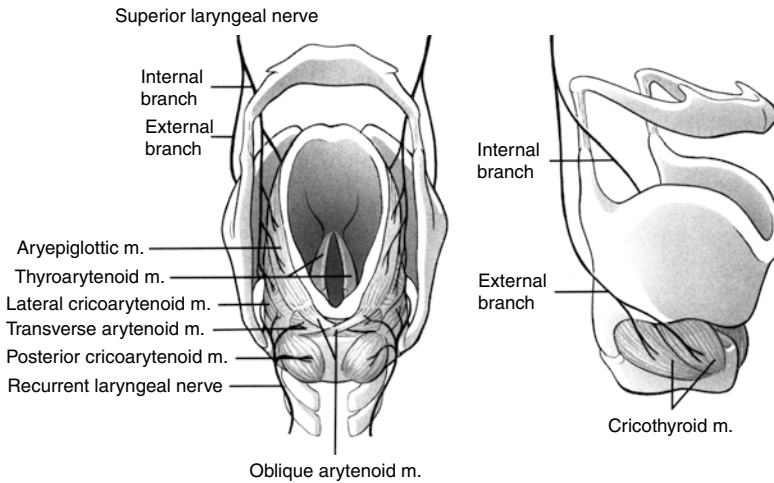


Fig. 4.4 The intrinsic laryngeal muscles and their innervation are shown. The *left panel* shows from bottom to top the posterior cricoarytenoids, the sole abductors of the larynx, and the abductors: the thyroarytenoids, the lateral cricoarytenoids, the transverse and oblique arytenoids, and the aryepiglottic muscles. All of these muscles are

supplied by the recurrent laryngeal nerve (X). The internal branch of the SLN is sensory, while the external SLN branch is motor for the cricothyroid muscles (*right panel*) (From O'Connor, D. Reproduced with permission from Myer et al. (1995). Redrawn by agreement with Springer-Verlag)

4.1.4.1 Laryngeal Opening and Closure in Airway Protection and Breathing

4.1.4.1.1 Laryngeal Closure and Airway Protection

Protection of the subglottic airway is a centrally controlled major task of “breathing.” Laryngeal stimulation can trigger a clearing response, e.g., an expiration reflex or a cough, or can result in airway closure. Laryngeal closure occurs at the level of the epiglottis, at the vestibular folds, and at the vocal folds. This triple mechanism has been likened to closure of a nutcracker, an analogy whose accuracy is all too evident to intensivists faced with laryngospasm (Fink 1973).

4.1.4.1.2 Eupnea: Glottic Aperture Size and Flow/Volume Control

In adult humans the glottis opens maximally during inspiration, closes gradually to a minimum about three quarters through expiration, and then opens again in late expiration (England et al. 1982a). Glottic resistance is least at peak inspiration, increases as expiration progresses, and then decreases in late expiration to minimize inspiratory flow resistance with the onset of pump

muscle activity (England et al. 1982a). There is no sensation of expiratory glottic closure in eupnea. Accurate, rapid laryngeal opening and closure maintains an optimal subglottic airway volume, ensures tidal volume changes that enable gas exchange, and enhances airway patency and surfactant secretion. The smooth tidal flow pattern, produced by laryngeal and diaphragmatic activities interacting with the mechanics of the respiratory system, avoids tissue exposure to acceleration or deceleration injuries.

4.1.4.1.3 Integrative Central Control and Effects

The same laryngeal intrinsic muscles are involved in all laryngeal functions emphasizing that the central coordinations of the motor acts of breathing are truly integrative, a fact also stressed by the impacts that laryngeal sensory inputs and the resultant vagal outputs have on the cardiovascular system. Laryngeal closure is important for other motor acts, e.g., effective lifting. Central control of breathing is linked to emotions. It is of note that in laughter the order of abductor–adductor activities seen in breathing is reversed (Luschei et al. 2006). Eastern philosophies combine

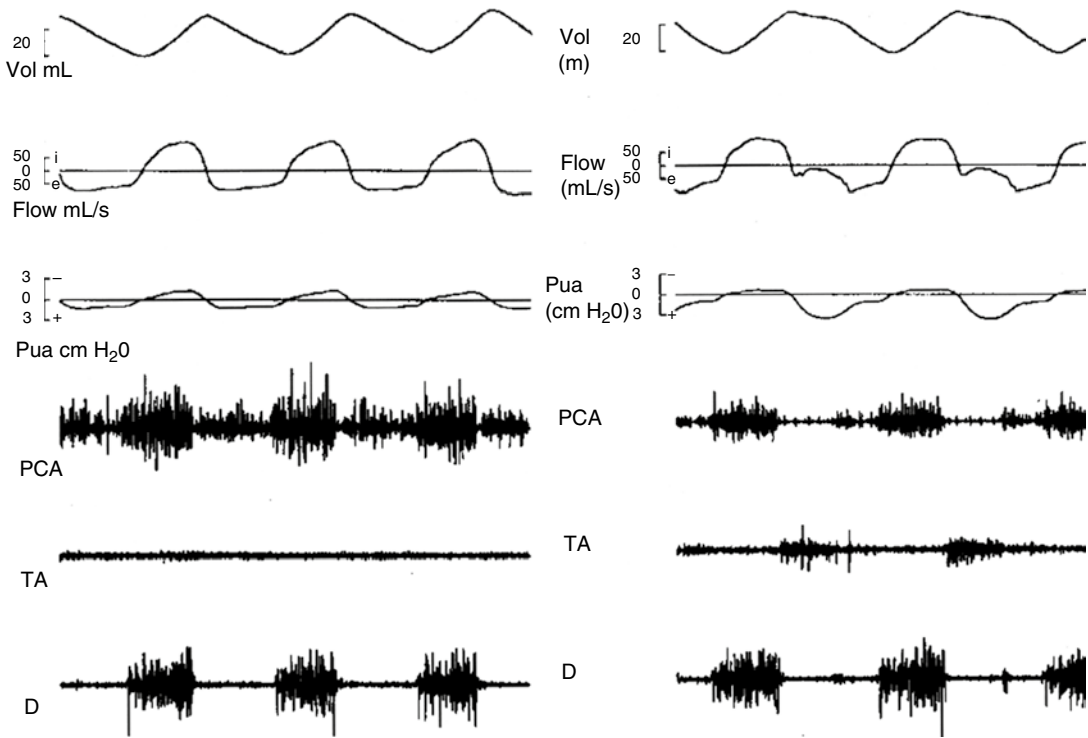


Fig. 4.5 This figure demonstrates the breathing cycles during eupnea and grunting in newborn lambs, showing the relationships between the EMGs of the posterior cricoarytenoid (PCA) muscles, those of the major adductors,

the thyroarytenoid (TA) muscles, and those of the diaphragm (D), together with flow, volume, and trans-upper airway pressure changes (Reproduced with permission from Hutchison et al. (1993))

breathing and vocalizations in practices aiming to augment metabolic and mental well-being.

4.1.4.2 Laryngeal Intrinsic Muscles and Control in Breathing

Understanding the actions of the laryngeal intrinsic muscles is a necessary first step in gaining insights into the nature of the central control of breathing. The posterior cricoarytenoids (PCA) are the sole abductors of the vocal cords. There are several adductors, with the thyroarytenoids (TA) being the major ones (Fig. 4.4). Some adductors, the cricothyroid and the vocalis part of TA, enhance abduction by tensing the vocal cords. This restricts vertical movement, improving flow control in the more horizontal plane. The magnitude of abductor activity exceeds that of the adductors when glottic size is increased and vice versa, consistent with relationships between glottic size and flow resistance (England et al. 1982a; Insalaco et al. 1990; Kuna et al. 1988). Animal

studies indicate that, in general, glottic opening and closing are achieved by reciprocal laryngeal abductor and adductor activities (Fig. 4.5) (Bartlett 1989; Harding 1986; Hutchison et al. 1993). Concurrent actions of laryngeal abductor and adductor muscles during inspiration and expiration may occur in adult humans, but their nature is unknown (Insalaco et al. 1990; Kuna et al. 1988, 1990).

4.1.4.2.1 Laryngeal Intrinsic Muscles in Eupnea and Grunting

During eupnea the inspiratory outline of the PCA EMG resembles the flow pattern, while the ramp shape of the diaphragm EMG relates to the inspired volume trace (Hutchison et al. 1993). In animals little expiratory TA activity is seen, and trans-upper airway pressure is minimal (Fig. 4.5). In eupneic expiration in adult humans, PCA activity diminishes, but some TA activity is present “rounding off” the early expiratory volume

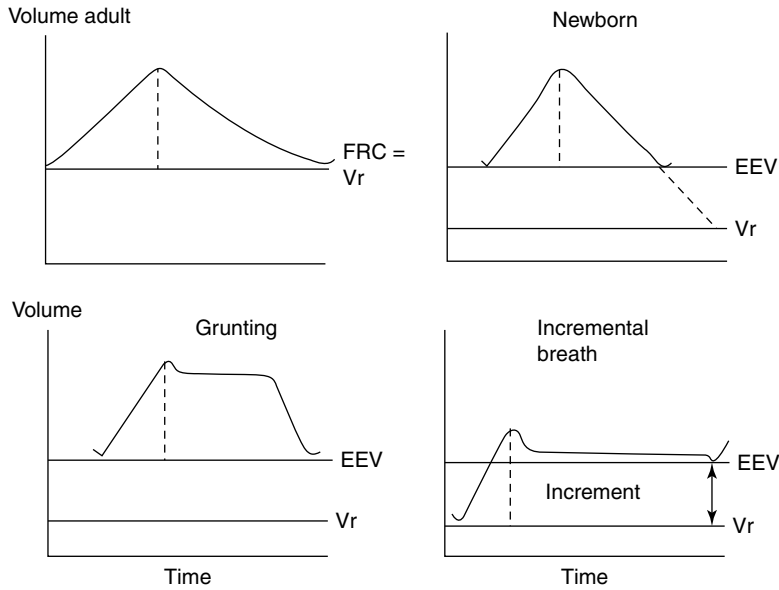


Fig. 4.6 Volume–time diagrams of adult and neonatal lung volumes are shown. The dashed line in each tidal volume separates inspiration from expiration. At rest (relaxation), the end-expiratory lung volume (EEV) of the adult (*top left*) is termed the functional residual capacity (FRC). It is a relaxation volume (V_r). In the newborn (*top right*) the V_r is low in comparison with that of the adult. The neonate actively maintains an EEV above V_r . The

grunting breathing pattern (*bottom left*) maintains lung volume above the EEV for variable periods of expiration before the volume returns to the EEV. The incremental pattern of breathing (*bottom right*) maintains lung volume above the EEV throughout expiration and, using laryngeal and diaphragmatic activities, achieves a true increment in lung volume (Reproduced with permission from Hutchison and Bignall (2008))

trace, but without the flow retardation or trans-upper airway resistance patterns typical of grunting (Kuna et al. 1988) (Fig. 4.5). Time delays exist between EMG and mechanical flow changes (Hutchison et al. 1993). The timing delays differ in eupnea and grunting, reflecting different mechanoreceptor feedbacks and central outputs that affect function (Fig. 4.5) (Hutchison et al. 1993).

Clinically, grunting is the expiratory noise produced when air flows through a partially closed glottis (Harrison et al. 1968). Total glottic closure is silent but sensed. Physiologically, grunting is a breathing pattern seen throughout life. It consists of a spectrum of degrees and timings of expiratory laryngeal closure, associated with volume retention and increased subglottic pressure, followed by laryngeal opening with a rapid return to baseline end-expiratory volume (EEV) (Figs. 4.5 and 4.6) (see Sect. 47.3.1) (Hutchison et al. 1993). In newborns with respiratory distress, Harrison et al. showed that when grunting was prevented by endotracheal intubation, without positive end-expiratory pressure

(PEEP), their oxygenation worsened (Harrison et al. 1968). This finding established the role of airway PEEP and likely influenced the introduction of CPAP therapy. Harrison et al. also focused on venous return (Harrison et al. 1968), stressing the importance of cardiac function in grunting. The outline of the volume–time trace in grunting (Figs. 4.5 and 4.6) resembles that of a volume with a prolonged inspiratory time, as used in artificial ventilation to improve oxygenation. Pre-surfactant, this strategy reduced the required peak inspiratory pressure and decreased the incidence of bronchopulmonary dysplasia. Today, the maintenance of subglottic volume, the “open lung” approach, is a fundamental tenet of all ventilatory support. In keeping with the concept of alveolar interdependence, airway volume recruitment is achieved not by a maximal prolonged inflation but with an augmented breath (sigh) followed by an expiratory hold, mimicking the volume–time profile of grunting or of airway pressure release ventilation. Spontaneous sighs can be biphasic, with inspiration being

interrupted briefly by laryngeal closure. This mechanism may reset vagal afferent feedback, avoiding a Hering–Breuer inflation reflex and possible loss of the acquired volume (see Sect. 47.3.1). In summary, human and animal data emphasize the importance of laryngeal control of expiratory subglottic airway volume. This central control strategy whereby airway pressure is dependent upon volume control has been shown by the study of bubble physics to produce a more stable mechanical system (Hildebrandt 1974). Thus, coordinated central control of laryngeal and pump muscles is a major focus in the control of breathing. This knowledge can be applied in respiratory support (Hutchison and Bignall 2008).

4.1.4.3 Laryngeal and Pump Muscle Breathing Patterns in the Fetus and Newborn

Behavioral state is a major controlling factor of breathing pattern. In fetal lambs, during the high-voltage electrocorticogram (ECoG) state, apnea (no phasic laryngeal abductor or diaphragmatic activities) and tonic laryngeal adductor activity occur. Laryngeal adductor activity can be enhanced by laryngeal contact with cooled lung liquid, by fetal movements, by “arousals,” by swallowing, by uterine contractures, and by fetal hypoxemia. In the low-voltage ECoG state, laryngeal and diaphragmatic activities are similar to those seen postnatally (Harding 1986). Hypercapnia mainly enhances fetal breathing in the low-voltage ECoG state (Harding 1986). In general, active laryngeal retardation of lung liquid egress is reported in the absence of fetal breathing movements and is related to lung growth (Harding 1986). Stimulation of the superior laryngeal nerve (SLN) produces laryngeal closure (Harding 1986) that will prevent aspiration of noxious material, e.g., meconium. The coordination of the acts of fetal swallowing (Harding 1986) and “inspiratory” activities of the respiratory muscles stresses the developmental importance of the controller’s ability to switch patterns rapidly between upper airway closure (laryngeal adduction) with lack of diaphragmatic activity (apnea) and laryngeal abductor and pump activities (see Sect. 47.3.1).

Airway volume is high in the fetus compared to the newborn. It has been speculated that during different fetal behavioral states, the brain is setting the homeostatic limits for high and low airway volume to prepare the fetus for the major needs of subglottic volume control at birth (Hutchison 2007) (see also Sect. 47.3.1). Life’s greatest airway volume challenge, the establishment and maintenance of an air-filled airway at birth, is usually overcome without a hitch by breathing patterns whose complexities exceed those used during the majority of adult life. At birth, an incremental breathing pattern retains more inspired volume than is expired (Fig. 4.6) (Hutchison et al. 1994). Incremental breathing shares features with grunting with the addition of timing changes in laryngeal and pump muscle activities at end-expiration when the onset of pump muscle activity occurs before laryngeal muscles open the glottis fully. The result is a decrease in expired volume and an increase in EEV (Hutchison et al. 1994). This incremental mechanical process is aided by the airway stability accrued from the increased end-expiratory positive subglottic pressure that limits the development of a negative airway pressure during inspiration. Given their tendency to chest wall distortion, it is not surprising that incremental breathing can occur in preterm neonates (Eichenwald et al. 1992). Incremental breathing is also seen in gasping during acute cerebral hypoxia–ischemia (Hutchison et al. 2002). Gasping is typified by brief laryngeal abductor and pump muscle activities followed by long periods of laryngeal adductor activity with apnea (Hutchison et al. 2002). Subglottic pressure is increased, maintaining airway volume and likely promoting autoreuscitation (Hutchison et al. 2002).

4.1.5 Control of Coordinated Laryngeal and Pump Muscle Activities

4.1.5.1 Laryngeal Protective, Lower Airway and Chest Wall Afferents

Nasal and laryngeal afferent inputs alter laryngeal abductor and adductor activities and thus glottic size. The laryngochemoreflex (LCR), whose afferent pathway is the SLN, results in

protective responses, including swallowing, apnea, obstructed respiratory efforts, cough, hypertension, and arousal from sleep (Thach 2008). An obstructive apnea with bradycardia results if the LCR stimulus is persistent, especially in the immature or depressed brain. This LCR response alters with age – coughing becomes the major response. However, acquisition of a viral infection in infancy can rekindle its potency (Thach 2008). It is augmented by hypoxemia and anemia and has been implicated in apnea of prematurity and SIDS (Thach 2008) (see Sect. 47.3.1).

Other laryngeal SLN afferents, including those from mechanoreceptors, drive receptors, and temperature receptors, affect laryngeal intrinsic muscle activities. Although SLN section does not alter the eupneic breathing pattern, these afferents are important. Upper airway bypass can alter the inspiration-inhibition Hering–Breuer reflex. Application of acid to the larynx in animals, mimicking chronic aspiration, alters the subsequent response to an applied airway load (see Sect. 47.3.1). During noninvasive ventilation, nonsynchronous delivery of airflow to the upper airway in neural expiration results in laryngeal closure (Rodenstein 2004; Scharf et al. 1978). Thus, noninvasive ventilation and pacing of a paralyzed diaphragm should be applied synchronously with neural inspiration (Rodenstein 2004; Scharf et al. 1978).

In intact animals, compensatory glottic abduction follows single-breath total occlusion of inspiration or expiration at the mouth/nose. During the unimpeded expiration following a single inspiratory occlusive load, unopposed TA activity can produce laryngeal closure. Thus when no air enters the lung, a compensatory reflex mechanism can prevent expiratory volume loss, maintaining absolute subglottic volume. Lower airway afferent inputs affect glottic size (Bailey and Fregosi 2006). Stretch receptor discharges, induced by PEEP, decrease expiratory TA activity (Harding 1986). By contrast increased expiratory glottic adduction follows rapidly adapting receptor stimulation, e.g., with deflation or irritant stimulation secondary to a pneumothorax (Bartlett 1989), or follows C-fiber stimulation, e.g., with experimental pulmonary edema (Bartlett 1989). Direct and

indirect stimulation of chest wall muscle afferents can invoke several flow patterns involving glottic closure (Bartlett 1989; Stecenko and Hutchison 1991).

While pseudoasthma can be fabricated by partial glottic closure (Rodenstein 2004), matching laryngeal control of flow pattern to maintain optimal subglottic airway volume may explain changes reported with true increased airway resistance. Subglottic inspiratory flow limitation in croup is associated with expiratory flow resistance, probably glottic in origin (Argent et al. 2008). Increased lower airway resistance in adult asthmatic patients induces a breathing pattern characterized by laryngeal expiratory flow retardation (Collett et al. 1983; Sekizawa et al. 1987). In adults, resistive loads applied at the mouth also decrease expiratory glottic size (Brancatisano et al. 1985). This change may occur immediately, suggesting that resistive loading, unlike total occlusive (elastic) loading, produces sudden flow changes that stimulate airway receptors to cause laryngeal adduction (Brancatisano et al. 1985). Therapy with CPAP reverses the expiratory laryngeal adduction in some asthmatic subjects, suggesting that airway pressure changes may alter the dynamics between stretch receptor and irritant receptor stimulations, thus changing the breathing pattern (Collett et al. 1983). In normal adults a voluntary deep breath can decrease laryngeal resistance and lower airway resistance (Sekizawa et al. 1987). By contrast, bronchoconstrictive stimulation in normal adults can result in inspiratory and expiratory glottic narrowing (Higenbottam 1980). An increased resistance to inspiratory flow may be advantageous in that more transpulmonary pressure is applied to opening a constricted peripheral airway. If lower airway volume and resistance changes affect laryngeal function, can absence of laryngeal control affect lower airway resistance? Laryngeal bypass during invasive ventilation is associated with atelectasis and with the development of increased lower airway resistance (Hutchison and Bignall 2008). The latter effect may stiffen the conducting airways and thus stabilize total airway volume but demand increased effort. In summary, the data reflect the importance of laryngeal subglottic volume control as a

determinant of lower airway resistance and point to interactions between lower airway afferents and coordinated laryngeal and pump muscle activities in this dynamic process (see also Sect. 47.3.1).

4.1.5.2 Central and Chemical Control

Central control of coordinated laryngeal and diaphragmatic muscle activities is determined by developmental stage, behavioral states, metabolism (temperature), central inputs, and centrally acting chemicals. Postnatally in lambs, increased expiratory TA activity with decreased PCA activity occurs during the NREM state. By contrast, expiratory TA activity in REM is mainly absent, while PCA activity is variable (Harding 1986). In normal adult humans, expiratory TA activity is absent during stable NREM, while expiratory PCA activity decreases in NREM and is variable in REM (Kuna et al. 1988, 1990). At all ages, expiratory TA activity occurs at arousal. Thus behavioral state is a key factor in subglottic airway volume control that, in turn, is important in sleep apnea.

Increased central drive, with hyperventilation and/or hypercapnia, promotes laryngeal abduction in inspiration and expiration in adults and term newborns, in whom increased PCA, diaphragmatic and intercostal muscle activities occur (Bartlett 1989; Insalaco et al. 1990; Kuna et al. 1994; Wozniak et al. 1993). Laryngeal adduction can occur during hypercapnic hyperventilation in preterm neonates, probably due to chest wall distortion (but see also Sect. 47.3.1) (Eichenwald et al. 1993). This adduction also occurs in adults at the mechanical limits of airway volume (Brancatisano et al. 1983). In general, however, increased central drive decreases laryngeal resistance unless mechanical limitations are present.

Decreased central drive with hypocapnia diminishes expiratory glottic size and is associated with periodic breathing in adults (Kuna et al. 1993; Rodenstein 2004). Laryngeal closure has been noted in human newborns and infants with apnea or suspected apparent life-threatening events (Ruggins and Milner 1991, 1993). During central apnea and periodic breathing in lambs, expiratory TA activity is noted (Praud 1999). In

depressed human infants at birth, laryngeal closure can block intubation, and, in lambs, acute cerebral hypoxia–ischemia results in expiratory TA activity with laryngeal closure (Hutchison et al. 2002). Centrally acting depressant drugs diminish central drive and, in lambs, produce laryngeal closure with apnea (Praud 1999). In former preterm infants, up to ~55–60 postmenstrual weeks, exposure to anesthesia and/or operative stress can result in apnea postoperatively (see Sect. 47.3.1). Thus, the intensivist should avoid hypocapnia during noninvasive ventilation and be aware that central depression can result in apnea with glottic closure.

Hypoxia stimulates expiratory laryngeal abduction and increases ventilation in human adults and newborn lambs (England et al. 1982b; Insalaco et al. 1990; Praud et al. 1992). In lambs, the increase in ventilation is dependent upon carotid body input – a sudden decrease in that input induces expiratory TA activity (Praud et al. 1992). However, animal and human data indicate that the effects of carotid body input vary depending upon central state and the presence/absence of other inputs (de Burgh Daly et al. 1979). If animals are vagotomized and paralyzed, direct carotid body stimulation can induce expiratory TA activity, and exposure to hypoxia after airway vagal blockade or intrathoracic vagal section results in laryngeal adduction (Bailey and Fregosi 2006). In adult humans, the degree of expiratory glottic adduction with hypoxia exceeds that during hypercapnia (England et al. 1982b). Thus, it is argued that the “pure” carotid body reflex response is laryngeal expiratory adduction that will retain airway volume and promote oxygenation. This pure response can be countered by the presence of ventilation which increases airway stretch receptor feedback that results in an overall expiratory laryngeal abduction response. In the author’s view, a unifying explanation for the diverse findings with hypoxia is that the effect of carotid body input is to augment the central coordinated output to laryngeal and pump muscles that is selected under different conditions (see Sect. 47.3.1). When central depression exists, protective inputs and/or absence of volume-related inputs produce an apneic response

with glottic closure that is augmented by hypoxia. This can be seen in the “vagal” preterm infant who is sedated for a surgical procedure. At intubation laryngeal closure and apnea/bradycardia can be triggered. If hypoxemia ensues, the problems are aggravated. When tidal ventilation and airway volume feedback are restored, the impact of any ongoing hypoxemia is to augment breathing. Hering and Breuer found that their volume-related reflexes were active even with hydrogen breathing. This fits the modern focus on ventilation for resuscitation from asphyxia.

Conclusion

This chapter of upper airway physiology for the pediatric intensivist has focused on motor and specifically on laryngeal aspects relevant to the control of breathing patterns. The major message is that upper airway physiology is involved in all aspects of “breathing”: protection, volume homeostasis, and ventilation; its functional impact covers the entire airway, from the nose to the alveolus. Understanding upper airway physiology can guide and improve therapy, while therapy can aid a return to normal homeostasis or detract from it. Current knowledge of upper airway physiology has had major implications for the application of invasive and noninvasive ventilatory support. Much remains to be learned from the interactions between physics and biochemistry in the entire airway and how they affect breathing patterns.

Essentials to Remember

- The upper airway plays roles in all the extended functions of breathing, namely, in airway protection, in the control of supra- and subglottic volumes, and in tidal ventilation.

- Nasal functions include air conditioning and airway protection. Stimulation can result in profuse secretions, altered patency, and the cardiorespiratory dive reflex. Obstruction can affect gas exchange markedly; thus, a rapid switch to oral breathing is advantageous.
- Pharyngeal patency can be altered in sleep. Nonnutritive swallowing is vital to minimize aspiration. Therapy with CPAP improves pharyngeal patency in OSA but may alter pharyngeal clearing mechanisms and increase gastric air.
- Laryngeal closure can protect the airway rapidly. Laryngospasm can be hard to treat.
- Controlled expiratory laryngeal closure modifies airflow and subglottic airway volume in normal breathing, at the establishment of airway volume at birth or when airway volume is threatened by mechanical, chemical, or central changes.
- Intrinsically or extrinsically induced changes in central state alter the laryngeal motor outputs in response to mechanical or chemical inputs.
- Understanding how laryngeal motor functions affect breathing patterns, airway pressures, and gas exchange is at the core of many technical and procedural advances in the provision of resuscitative measures and of invasive and noninvasive respiratory support.

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4.2 Mechanics of the Lung, Airways, and the Chest Wall

Paul D. Robinson and J. Jane Pillow

Educational Aim

To describe the principal components of respiratory mechanics of the airways, lungs, and the chest wall and the developmental and environmental considerations that impact on these measurements in the neonatal and young child

4.2.1 Background

The mechanical properties of the respiratory system are a critical component of the chain of events that result in translation of the output of the respiratory rhythm generator to ventilation. A comprehensive understanding of respiratory mechanics is therefore essential to the delivery of optimized and individualized mechanical ventilation. This chapter describes the basic elements of respiratory mechanics and reviews the developmental changes in the airways, lungs, and chest wall that impact on measurement of respiratory mechanics with advancing postnatal age.

During spontaneous breathing, the forces driving inspiration are generated by the inspiratory muscles, whereas during mechanical ventilation, the forces are generated by the ventilator or by a combination of the ventilator with spontaneous inspiratory muscle contributions. The inspiratory muscle pressure needs to be sufficient to overcome three major mechanical properties of the respiratory system: *elastance* (E) (to overcome tissue forces required to change the lung volume (V)), *resistance* (R) (to overcome resistance to flow (V')), and *inertance* (I) (for acceleration (V'') of gas volumes). Elastance is often considered in terms of its inverse, the compliance (C). The total pressure (P_{total}) generated is equal to the sum of the elastic (P_{el} , proportional to volume and $1/\text{compliance}$), resistive (P_{res} , proportional to flow and resistance), and

inertive (P_{in} , proportional to acceleration and inertance) components:

$$P_{\text{total}} = P_{\text{el}} + P_{\text{res}} + P_{\text{in}} = (V \times 1/C) + (V' \times R) + (V'' \times I) \quad (4.1)$$

Although pressure losses to inertia are considerable during high-frequency ventilation, the inertive component is normally a small portion of P_{total} at normal breathing frequencies and can be effectively neglected. Thus the equation driving flow during normal respiration can be simplified:

$$P_{\text{total}} = P_{\text{el}} + P_{\text{res}} + P_{\text{in}} = (V \times 1/C) + (V' \times R) \quad (4.2)$$

Nonetheless, the linearized relation of driving pressure to volume and flow does not fully characterize the pediatric respiratory system: Resistance and compliance are both dependent on volume, volume history, and flow, particularly in the very small or premature neonate. Further, the simplified equation does not fully incorporate the complexities of the respiratory system.

Almost all the tests used to measure respiratory mechanics in the infant and pediatric population have been developed in adults and then adapted for younger subjects. Measurements of respiratory mechanics are most appropriately corrected to lung volume, such as functional residual capacity (FRC). In the absence of a measure of FRC, measurements of respiratory mechanics made in infancy are often related to body size (e.g., height/length or weight). Measurements at the body surface are necessary to include the contributions of the chest wall. The chest wall contribution to respiratory mechanics can be isolated, by subtraction of the pleural measurements from those obtained at the body surface (e.g., airway opening).

4.2.1.1 Passive Tests of Respiratory Mechanics

The respiratory system is in a passive state when there is no inspiratory muscle activity ($P_{\text{mus}}=0$). A passive condition is present in the paralyzed patient but can also occur without paralysis following hyperventilation (Mortola 2004). Under passive conditions, resting lung volume is determined by

two opposing forces. The outward recoil of the chest wall results from the elastic characteristics of the diaphragm/abdomen and of the rib cage. The outward recoil of the chest wall directly opposes the inward recoil of the lung. Inward recoil is determined by the viscoelastic properties of the lung, including the mechanical properties of the lung tissues, and the collapsing pressure generated at the alveolar air–liquid interface.

During spontaneous breathing, the passive respiratory mechanics can be measured using occlusion techniques. Occlusion of the airways at lung volumes above the resting lung volume relaxes the respiratory muscles by stimulating the slowly adapting stretch receptors and the vagally mediated Hering–Breuer inflation reflex. Passive tests assess the mechanical properties of the entire respiratory system. Simultaneous measurement of transpulmonary pressure allows measurement of respiratory system compliance (C_{rs}) to be partitioned into lung (C_L) and chest wall (C_w) components. Transpulmonary pressure (P_{tp}) is derived from the difference in pressure at the airway opening (P_{ao}) and pleural pressure (or elastic recoil pressure, P_{el}), measured using an esophageal balloon, liquid-filled catheter, or miniature pressure transducer.

$$P_{ao} = P_{tp} + P_{el} \quad (4.3)$$

Other passive measurements of respiratory mechanics include forced expiratory maneuvers to provide measures of maximal flow at FRC ($V'_{max,FRC}$) (Lum et al. 2006a). Partial forced expiratory flow–volume curves in infants are obtained by rapid compression of the chest through end-inspiratory inflation of a jacket placed around the chest and abdomen. During tidal breathing, this rapid thoracoabdominal compression (RTC) technique provides a $V'_{max,FRC}$ that is similar to forced flows at low lung volumes (e.g., maximal expiratory flow $MEF_{25\%FRC}$). Modification of the RTC technique by raising lung volume of the infant towards total lung capacity (so-called raised volume RTC or RVRTC) allows assessment of forced expiratory flows over a more extended range of volumes. Reported measures include forced vital capacity (FVC) and forced expiratory volumes after defined time periods (e.g., 0.4, 0.5, or 1 s,

termed $FEV_{0.4}$, $FEV_{0.5}$, and FEV_1 , respectively) and the ratio of these values e.g., (FEV_t/FVC) , where t is the time period chosen).

4.2.1.2 Dynamic Tests of Respiratory Mechanics

In contrast, dynamic tests of respiratory mechanics allow the relative contributions of the airways and lung tissues to be partitioned, in addition to separately identifying the chest wall contribution to airway and tissue mechanical properties. Dynamic mechanics derive mechanical variables from analysis of dynamic waveforms obtained either during normal (tidal) breathing or via imposed oscillatory waveforms. During tidal breathing, multilinear regression is used to determine dynamic respiratory system compliance ($C_{dyn,rs}$) and resistance (R_{rs}). Kano and colleagues showed that consideration of volume dependence is important when using this approach to assess dynamic mechanics during mechanical ventilation. Consideration of volume dependence is important because ventilatory settings may “push” the pressure–volume curve onto the flattened upper portion of the curve (Kano et al. 1994). In the overdistracted lung, fits obtained by multilinear regression are improved by the inclusion of a volume-dependent elastance term in the regression model:

$$P_{ao} = (E_1 + E_2 V) V + R_{rs} V' + P_{A,EE} \quad (4.4)$$

where P_{ao} is the airway opening pressure, V is the tidal volume, $E_1 + E_2 V$ is the total elastance over the cycle (E_1 and $E_2 V$ representing the volume-independent and volume-dependent portions of elastance, respectively), and the final term $P_{A,EE}$ represents the alveolar pressure at end-expiration.

An important consideration during the interpretation of dynamic respiratory mechanics is the concept of frequency dependence. Kano showed that increasing the ventilation rate from 30 to 80 breaths/min in a group of near-term newborn infants increased E_{rs} and R_{rs} by a mean of 8.3 and 17.5 %, respectively (Kano et al. 1994). Frequency dependence and the mechanical properties of the respiratory system under normal tidal breathing conditions are also determined using forced oscillatory techniques (FOT). These techniques are

essentially noninvasive and are especially useful in infants and children as no active subject cooperation is required. The technique involves application of a pressure waveform (forcing function) to the airway opening and measurement of the resultant flow. The measured impedance reflects the complex viscoelastic resistance of the respiratory system (Z_{rs}). Simultaneous measurement of the transpulmonary pressure and hence chest wall impedance (Z_w) allows determination of the lung impedance (Z_L) by subtraction. The impedance (Z) can be separated into the resistance (R_{rs}), the impedance component in phase with flow, and reactance (X_{rs}), representing the impedance components in phase with volume (elastance) and acceleration (inertance).

The low-frequency forced oscillation technique (LFOT) measures impedance over a range of frequencies (usually ~ 0.5 – 20 Hz). LFOT is obtained in infants by invoking the Hering–Breuer inflation reflex to inhibit temporarily any respiratory muscle activity, during which brief time (6–10 s) the LFOT signal is applied. Fitting the constant-phase model to the resultant pressure and flow data permits partitioning of respiratory mechanics into frequency-independent airway resistance (R_{aw}) and airway inertance (I_{aw}) and a constant-phase tissue component. This constant-phase tissue component is described by $[(G - jH)/\omega\alpha]$, where G and H are coefficients for tissue damping and elastance, respectively, ω is angular frequency, and α determines the frequency dependence of the real (pressure change in phase with flow) and imaginary (pressure change in phase with volume) parts of the impedance] (Hantos et al. 1992a).

The interrupter technique provides a further option to assess partitioned mechanics. The interrupter technique involves measurement of changes in airway opening pressure after a mid-expiratory occlusion, which is used to calculate airway resistance (R_{aw}). After airway occlusion at mid-expiration, there is a biphasic change in P_{ao} : the immediate rapid rise in P_{ao} represents the resistive pressure drop across the conducting airways and is followed by a secondary slower increase in P_{ao} (often referred to as P_{dif}) generally attributed to stress recovery in the respiratory tissues (lung and chest wall) and gas redistribution

associated with ventilation inhomogeneity (Bates et al. 1988). A major limitation of this technique is that it requires mechanical ventilation and paralysis to obtain reliable data.

4.2.2 Developmental Considerations

Particular challenges for lung function testing in infants and children include the marked developmental changes occurring over the first months and years of life. Additional considerations include position, sleep state and sedation, and feasibility of individual tests given minimal capacity of these age groups for active cooperation and preferential nasal breathing (Stocks and Hislop 1996). Thus, in contrast to the adult and older child, tests in infants are performed using a mask instead of a mouthpiece and nose clips.

4.2.2.1 Airway and Lung Development

Lung development represents a period of considerable change in both lung architecture and volume and is affected by several factors including genetic, in utero and postnatal environmental exposures, somatic growth, puberty, changes in muscularity, and ongoing alveolarization. Our understanding of the interactions between these factors is based on a mix of pathological and physiological data, which are predominantly cross-sectional in nature. Consensus between these studies is lacking. While some of the lack of agreement is attributable to technical approaches used by different authors, a comprehensive understanding of factors influencing respiratory mechanics over time can only be answered by strong longitudinal data, which are urgently required. These tests of lung mechanics provide us with essential insight into how tissue properties change with development, and a full understanding of the changes that occur during healthy development is an important step to detect the subsequent effects of disease and response of the individual to therapeutic interventions. Measurements need to be accompanied by accurate records of height (length) and weight to facilitate interpretation of longitudinal data.

4.2.2.1.1 Dysanapsis

Over the course of development, there is considerable remodelling of all of the structural components of the respiratory system, although the exact patterns of change in airways, alveoli, and blood vessels may differ with respect to each other. The term “dysanaptic growth” was originally introduced by Green et al. (1974) and describes the disproportionate but physiologically normal growth of the lung relative to the airways. In infancy, airway size relative to lung volume is larger than in older children and adults. There is considerable debate in the pediatric literature about the degree, extent, and stage of development to which biological variability of airway size to lung volume occurs. The data outlined in this chapter suggest that dysanapsis is a feature of all stages of postnatal lung development.

Whether disproportionate growth along the length of the airway tree occurs is less clear. Increased growth of the larger central airways, in relation to peripheral generations, has been described through the first year of life, after which point adult relative proportions are achieved and maintained through further growth (Horsfield et al. 1987). Disproportionate central and peripheral airway growth, however, is not a consistent finding in the literature (Hislop et al. 1972). The most rapid period of tracheal growth appears to occur during the first 4 years of life (Wailoo and Emery 1982). An elevated ratio of peripheral airway resistance to central airway resistance (and its contribution to total airway resistance) in young children compared to adults was originally proposed by Hogg et al. (1970), based on retrograde catheter measurements. The authors described relatively little change in the contribution of the central airways (those proximal to the 12th–15th airway generations) to conductance with age but marked increase in peripheral airway conductance from the age of 5 years of age. These changes were attributed to altered linear dimensions of the peripheral airways, based on morphometric data. The ratio of central to peripheral resistance can also be examined noninvasively by comparing measured forced expiratory flows (FEF) breathing air to FEF measured breathing a less-dense gas mixture

of 80 % helium/20 % oxygen (heliox). FEF measured breathing heliox is typically higher than during air breathing (e.g., 1.2–1.6 times at 50 % FVC). In older subjects with peripheral airway disease, this pattern is lost with ratios approaching parity (Cooper et al. 1983; Dosman et al. 1975). Density dependence data during infancy, in comparison to values reported in later life, appear to challenge the findings of Hogg et al. (1970). Davis et al. examined the changes in density dependence through the first 2 years of life (Davis et al. 1999). FEF 30–40 % higher were measured with heliox; although no relationship existed between density dependence and age, length, or FVC in the first 2 years of life (in keeping with Hogg et al. (1970)), the values obtained were similar to those reported across 16 other studies in older children ranging from school age to adulthood (summarized in Table 2 of the original manuscript (Davis et al. 1999)). These equivalent cross-sectional density dependence values suggest that there is *no* difference in the convective accelerative and turbulent pressure loss with age, supporting the notion that the ratio of resistance of the peripheral to the central airways is similar in infants, older children, and adults.

4.2.2.2 Sex Differences in Respiratory Mechanics

Sex-specific differences in respiratory mechanics are well recognized in infants and young children and are a particularly important consideration in forced expiratory maneuvers in infants. Airways are larger in females before puberty, and this difference is detectable from infancy (Tepper et al. 1986a; Hoo et al. 2002a): $V'_{\max, \text{FRC}}$ is approximately 20 % higher in girls over the first 9 months of life (Hoo et al. 2002a). Similar sex-dependent increases in $V'_{\max, \text{FRC}}$ are evident in preterm girls compared to preterm boys, suggesting such differences in lung function may be developmental rather than environmental in origin (Stocks et al. 1997). Larger lungs have been reported in males between the ages of 6 weeks and 14 years (Thurlbeck 1982). Presence and timing of the growth spurt is an important confounding factor, with lung growth occurring out of phase to somatic growth, especially in boys (Degroodt et al. 1986;

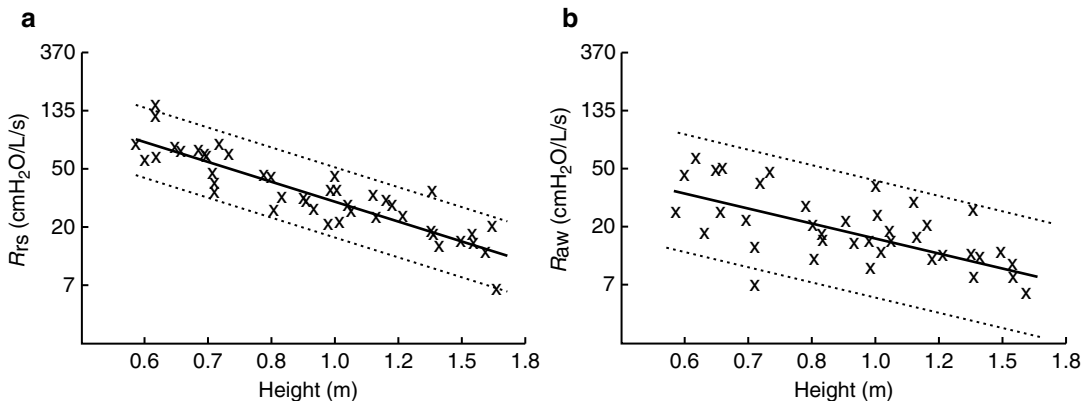


Fig. 4.7 Decreasing resistance of the respiratory system (R_{rs}) and airway resistance (R_{aw}) with increasing height. Cross-sectional data taken from 51 subjects (aged 3 weeks

to 15 years) (Lanteri and Sly 1993). Both resistance and height are plotted as natural log values but are labeled with absolute numbers for clarity

Quanjer et al. 1989; Schrader et al. 1984). Lung development in females is almost complete following menarche but continues throughout puberty in males (Neve et al. 2002).

4.2.2.3 Periconceptual and Intrauterine Exposures

There is increasing evidence that the periconceptual and intrauterine exposures impact on development of the respiratory system and consequently impact on respiratory mechanics in infancy and childhood. Factors known to influence lung mechanics after birth include maternal smoking, nutritional deprivation and intrauterine growth restriction, infection and/or inflammation, and maternal glucocorticoids. Prenatal exposure to nicotine may cause abnormal airway branching and dimensions as well as increase airway smooth muscle and collagen deposition resulting in reduced lung function at birth that persists into early adulthood regardless of postnatal exposure (Hayatbakhsh et al. 2009; Svanes et al. 2004). Lung function irregularities include airflow limitation, reduced FEV₁, and airway hyperreactivity (Sandberg et al. 2011; Wongtrakool et al. 2012). Chronic restriction of nutrients and/or oxygen in late pregnancy impairs development of the fetal small airways and lungs, including reduced numbers of alveoli that are also enlarged with increased septal wall thickness and basement membranes compared to nonexposed infants

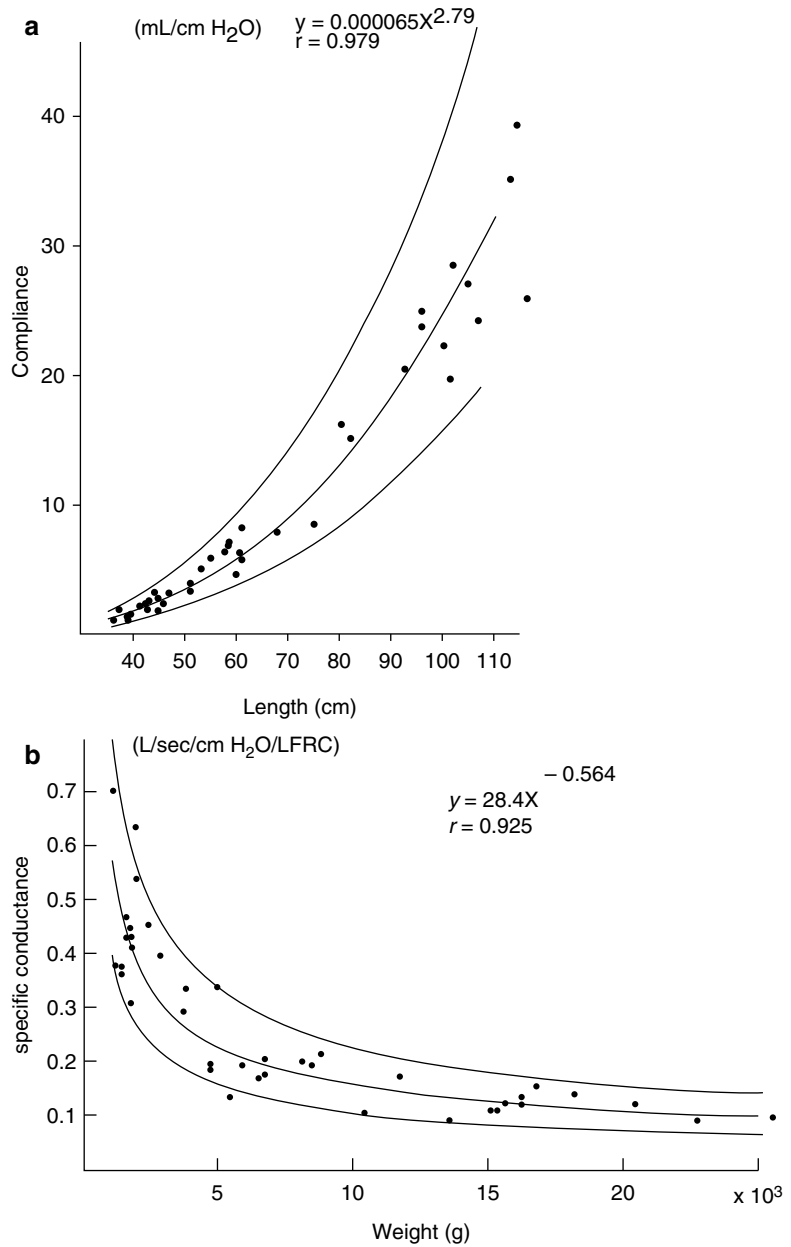
(Pike et al. 2012). Such differences in alveolar number can influence the subsequent rate of disease progression, including an accelerated rate of decline in FEV₁ with advancing age (Stocks and Sonnappa 2013).

4.2.3 Mechanical Properties of the Airways, Lung, and Chest Wall in Infancy and Childhood

4.2.3.1 The Airways

Several cross-sectional studies have looked at the changes in airway resistance (reflecting airway size) during childhood. Hall and colleagues using LFOT described a quasilinear decrease in R_{aw} with increasing length during infancy in 37 infants, including some with repeat measurements (Hall et al. 2000). Lanteri and Sly examined changes across the pediatric age range and also reported linear decreases in both R_{rs} and R_{aw} with increasing height (when plotted on a log-log plot) in 51 children (range 3 weeks–15 years) with healthy lungs (Fig. 4.7) (Lanteri and Sly 1993). Pooled data across the preschool age range reinforces the consistent relationship seen with increasing height (Beydon et al. 2007a). In a study of 40 subjects, across the first 5 years of life, Gerhardt et al. demonstrated an increase in lung conductance (the reciprocal of resistance), of approximately fivefold over the weight range

Fig. 4.8 Rapid increase in lung compliance (a) and rapid decrease in specific conductance (b), with increase in body length, based on cross-sectional data in 40 subjects in the first 5 years of life (Gerhardt et al. 1987a). The regression line (solid) and 95 % confidence interval (dotted lines) are shown (Reproduced with permission from the publisher)



examined (Gerhardt et al. 1987a). This increase occurred at a slower rate than the increase in FRC, which led to a rapid drop in specific conductance (Fig. 4.8b). This rapid decrease in specific airway resistance or conductance through early life has been described previously (Doershuk et al. 1974; Stocks and Godfrey 1977). Tepper et al. measured maximal FEF at FRC, from partial expiratory flow–volume

curves and corrected for changes in lung volume: they reported higher flows in the neonatal range which decreased to a steady value through the 2nd year of life, similar to those reported elsewhere in older children (Tepper et al. 1986a). Differential increases in anatomic dead space volume (twofold), compared to FRC (threefold), have also been shown in the pediatric population (Wood et al. 1971).

4.2.3.2 The Lungs

Rapid postnatal increases in lung volume are reported widely. FRC increases by a magnitude of 40 times (from 80 mL in infants to 3,000 mL in adults) (Dunnill 1982) and over ten times in total lung weight (Polgar and Weng 1979). The rapid growth of the distal lung, in comparison to relatively steady changes in airway dimensions, is a major feature of respiratory system development beyond birth. After the appearance of primitive saccules at approximately 28 weeks gestation, mature alveoli with secondary septa appear from 34 weeks gestation onwards. Alveolar multiplication was initially thought to cease at around 2 years of age (Thurlbeck 1982). More recent estimates indicate that increase in alveolar number continues until at least 8 years (Dunnill 1982). Recent advanced imaging studies using hyperpolarized helium magnetic resonance imaging (MRI) provide evidence of ongoing alveolar multiplication in adolescence (Narayanan et al. 2012). Increase in alveolar size (expansion) is also evident during infancy and childhood, with recent epidemiology studies suggesting lung size increases into early adulthood, when chest wall development is complete (Quanjer et al. 1989; Reid 1977).

Based on cross-sectional studies, specific lung compliance falls during early infancy before remaining relatively constant from the early pre-school years. Tepper et al., based on measurements of compliance from the linear portion of the static pressure–volume (PV) curve in almost 50 infants, described an increase in lung compliance over the age range studied, but decreasing specific lung compliance with increasing body length in the first 2 years of life (Tepper et al. 2001). Gerhardt et al. examined similar changes in 40 infants and children over the first 5 years of life. Lung compliance increased markedly (by ~20–25-fold) over the weight range examined (Fig. 4.8a) but in proportion to FRC, resulting in a constant-specific compliance over the first 5 years of life. The same pattern of findings was reported in 63 children aged 2–7 years (Greenough et al. 1986). This initial rapid period of alveolar growth is also supported by evidence from measurements using the interrupter technique and FOT. Lanteri and Sly showed a biphasic change

in P_{dif} with age: P_{dif} was highest in young infants, falling rapidly over the first 12 months, before increasing again after approximately 5 years of age (Lanteri and Sly 1993). Hall and colleagues, using LFOT measures of tissue mechanics derived by fitting data to the constant-phase model, showed that both tissue parameters G and H decreased in a quasihyperbolic manner with increasing length between 7 weeks and 2 years of age (Hall et al. 2000). The difference in the pattern of change in G and H compared to the change in R_{aw} with increasing length is further evidence of dysanapsis: tissue mechanical properties change more rapidly than airway mechanics over the first 2 years of life (Fig. 4.9).

4.2.3.3 The Chest Wall and Respiratory Musculature

The chest wall of the neonate and infant, and to a lesser extent the growing child, is especially compliant compared to the compliance of the chest wall in the adult subject. A highly compliant chest wall in infancy results in less opposition to the tendency of the lung to collapse, promoting a low residual lung volume and also distortion of the chest wall, resulting in a loss of volume during inspiration. The disproportionately high compliance of the chest wall compared to the compliances of the lung means that the compliance of the respiratory system (C_{rs}) is approximately equal to the compliance of the lung (C_{L}) during childhood, especially in neonates and infancy (Davis et al. 1988; Gerhardt et al. 1987a). Several active (dynamic) mechanisms of respiratory mechanics serve to partially compensate for the instability in FRC associated with a compliant chest wall and tendency for small airway closure during tidal breathing. Infants acutely increase their end-expiratory lung volume (EELV) and maintain it above resting lung volume by modulating (abbreviating) their expiratory time (Mortola and Saetta 1987) (Fig. 4.10a). In addition, they reduce expiratory flow through post-inspiratory activity of the diaphragm and inspiratory chest wall muscles (Kosch and Stark 1984) (Fig. 4.10b) (Lopes et al. 1981), stiffening the chest wall and by increasing laryngeal resistance ($\pm$ glottic closure) briefly (Kosch et al. 1988). Such dynamic modifications of respiratory mechanics occur via neural (vagal)

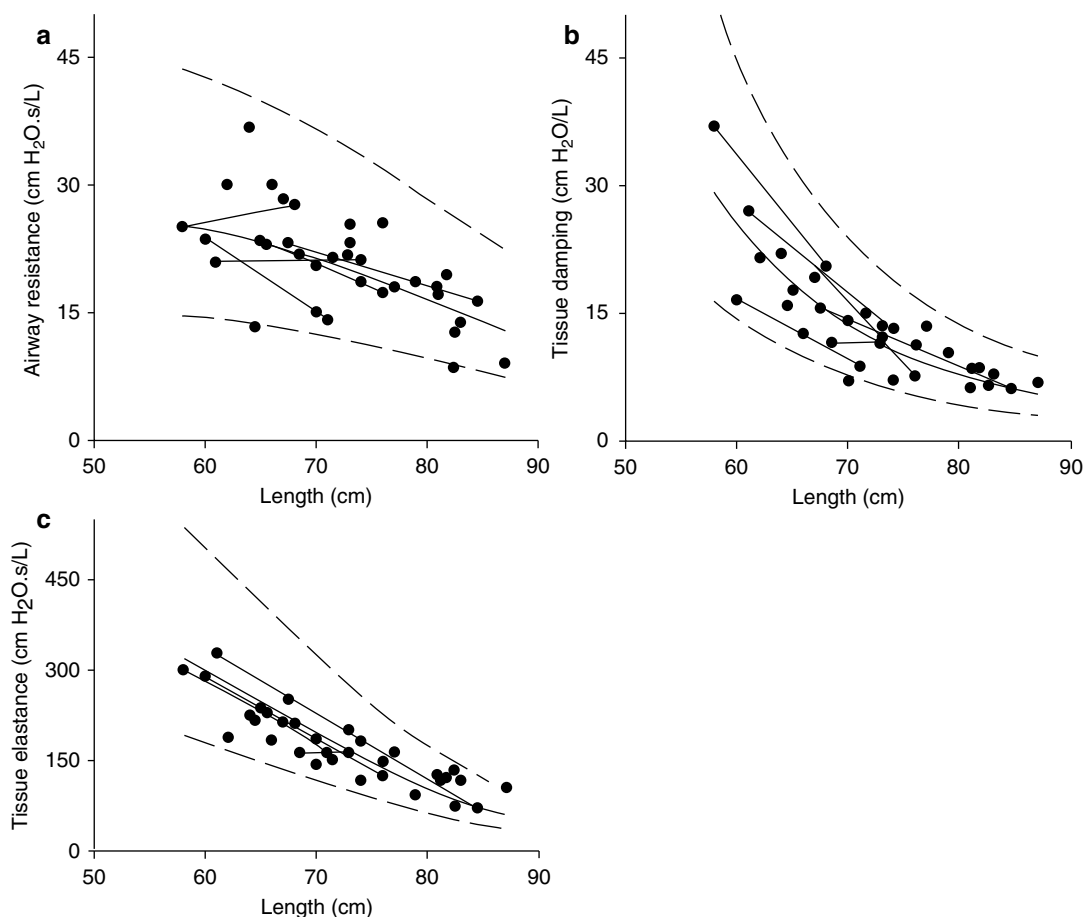


Fig. 4.9 Low-frequency FOT data plotted against length in 37 infants: airway resistance (raw, **a**), tissue damping (**b**), and tissue elastance (**c**). The greater rate of change suggested in tissue (**b**, **c**) compared to airway properties

(**a**) illustrates dysanaptic lung growth (Hall et al. 2000). Reprinted with permission of the American Thoracic Society (copyright © 2014 American Thoracic Society)

receptor-mediated reflexes. Restriction of lung function measurement to periods of quiet sleep is necessary to reduce the variability in measurements resulting from such dynamic processes (Henschen and Stocks 1999).

The changes in chest wall, lung, and respiratory system mechanics over the first 4 years of life were examined by Papastamelos et al., in 40 subjects (Papastamelos et al. 1995). The authors used a modified Mead–Whittenberger technique (Cook et al. 1957): manual ventilation overrode respiratory drive and relaxed the respiratory muscles, avoiding the need for intubation or induction of a Hering–Breuer reflex. In this cohort, the ratio of chest wall to lung compliance fell from a mean (SD) of 2.9 (1.1) to 1.3 (0.4) ($p < 0.005$). Chest

wall to lung compliance ratios are even higher in preterm infants (Gerhardt and Bancalari 1980). The stiffening of the chest wall, due to rapid rib ossification, increasing musculature, and altered chest wall configuration (Bryan and Wohl 1986; Mead 1979; Openshaw et al. 1984; Leiter et al. 1986), is such that near-adult values, where lung and chest wall compliance are equal (Mittman et al. 1965), are reached after the first year of life.

Stiffening of the chest wall over the first year of life allows the infant to shift its maintenance of FRC from dynamic elevation of EELV to a more passive mechanism achieved by the balance of outward recoil of the chest wall and inward recoil of the lung (Colin et al. 1989). Stiffening of the chest wall likely also explains the increase

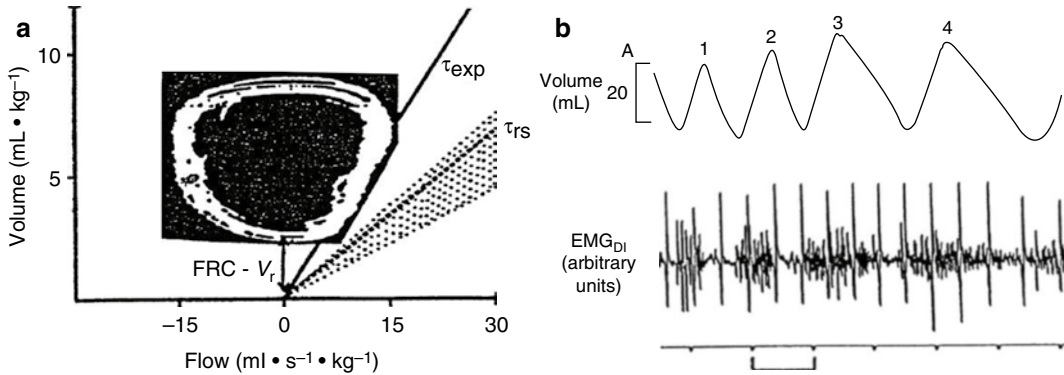


Fig. 4.10 Employment of active (dynamic) mechanisms to elevate end-expiratory lung volume (EELV) in infants. In (a), active prolongation of the respiratory system time constant (τ) is shown. The expiratory time constant (τ_{exp}) is shown as the slope of the measured expiratory limb of the tidal flow–volume curve (solid line). This is compared to the passive expiratory time constant (slope of the dotted line) measured after an end-inspiratory occlusion. The difference between the two slopes is generated due to active use of the respiratory muscles during expiration (“braking”). The mag-

nitude of difference between the active flow–volume curve-derived EELV (FRC) and the passive relaxation volume (V_r) reflects the degree of active (dynamic) mechanisms employed to elevate EELV. This active use of respiratory muscles is also illustrated in (b) from data collected in a separate infant study wherein diaphragm EMG activity of breaths three and four extends into expiration (Both figures reproduced with permission from the publishers (Mortola and Saetta 1987; Kosch and Stark 1984))

in P_{dif} in children after age of 5 years observed by Lanteri and Sly (Lanteri and Sly 1993). FRC as a proportion of total lung capacity (TLC) increases with age through childhood, in the majority (Engstrom et al. 1956; Mansell et al. 1977; Weng and Levison 1969), but not all (Schrader et al. 1988), studies to date. Residual volume (RV), as a proportion of TLC, also increases with age through childhood (Merkus et al. 1993), while closing capacity (measured using single-breath nitrogen washout) decreases significantly with age, as a proportion of TLC, converging towards RV (Mansell et al. 1977). This increased RV/TLC ratio suggests that increased stiffness of the chest wall is not entirely compensated for by increase in expiratory muscle force over time (Schrader et al. 1988). The study by Merkus et al. also highlighted the need to use TLC as a measure of lung growth and not FVC, due to the fact that an increasing RV/TLC with age led to errors in maximal expired flows due to measurement at progressively higher lung volumes (Merkus et al. 1993).

4.2.3.4 Summary

The postnatal period is characterized by ongoing rapid lung development, with differing rates of

growth seen in the airway, lung parenchyma, and chest wall. The dysanapsis that occurs between the components of the respiratory system has important consequences for measurements of lung mechanics performed during infancy and childhood. Accounting for these developmental changes and dysanapsis is necessary to optimize disease detection and subsequent assessment of an individual’s response to interventions. Insights into these changes are largely derived from cross-sectional studies, which have identified important sources of potential error in existing methodol-

Essentials to Remember

- The postnatal period is characterized by ongoing rapid lung development in all parts of the respiratory system (airways, lung parenchyma, and chest wall). The physiologically normal rate of change of the lung relative to the airways is disproportionate. This dysanapic growth pattern appears to be a feature of all stages of postnatal lung development.

- Passive measures of lung mechanics provide information about the mechanics of the entire respiratory system.
- Dynamic measures of lung mechanics allow partitioning of the lung and chest wall components to separately identify the chest wall contribution to airway and tissue mechanical properties.
- Standardization of the measurement technique is essential. Results generated are corrected for either lung volume (e.g., FRC) or, in the absence of this, a measure of growth (e.g., weight).
- A number of periconceptual, intra-uterine, and postnatal factors impact on the development and mechanics of the respiratory system. Important postnatal factors include maternal smoking, nutritional deprivation and intrauterine growth restriction, infection and/or inflammation, and maternal glucocorticoids.
- The rate of airway growth (detected by increases in conductance or decreases in resistance) is not as rapid as the rate of FRC increase with age. This greater relative increase in lung volume leads to a rapid decrease in specific resistance during early childhood.
- Postnatal alveolarization appears to now extend into adolescence. Rapid alveolar growth occurs during infancy leading to an initial fall in specific lung compliance, which reaches a plateau during ongoing lung growth. These changes are also evidenced by the changes seen in LFOT tissue parameters and interrupter technique-derived P_{dif} .
- The highly compliant chest wall of the infant leads to employment of active (dynamic) measures to maintain EELV above FRC. As the ratio of chest wall to lung compliance falls and reaches the adult values of parity beyond infancy, these gradually transition to more passive mechanisms as the chest wall stiffens through early childhood.

ogy. Strong longitudinal data are now urgently required to confirm these apparent patterns and answer the important questions that remain.

4.3 Respiratory Mechanics in Neonatal Pathologies

J. Jane Pillow

Educational Aims

- To describe flow (F), lung volumes (V), and respiratory pressure (P) measurements together with resistance (R) and compliance (C) measurements in neonatal respiratory diseases

4.3.1 Acute Neonatal Lung Disease

The predominant neonatal acute respiratory diseases include transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS) due to surfactant deficiency and/or structural immaturity, pulmonary interstitial emphysema (PIE), meconium aspiration syndrome (MAS), persistent pulmonary hypertension of the newborn, pneumonia, and congenital diaphragmatic hernia (CDH). As there are no reported measurements of lung mechanics or lung function for infants with PIE and pneumonia, they are not discussed further.

4.3.1.1 Transient Tachypnea of the Newborn

Transient tachypnea of the newborn (TTN) is characterized by delayed resorption of fetal lung fluid within the distal airspaces. The mechanical consequences of TTN include reduced lung volume (functional residual capacity, FRC) and consequently also decreased lung compliance (increased elastance), tidal volume, and respiratory rate (Benito Zaballos et al. 1989). Although increased interstitial fluid might be expected to increase lung tissue resistance, there are no reported studies of tissue resistance in infants with TTN.

4.3.1.2 Respiratory Distress Syndrome

Like TTN, RDS is predominantly a disease of the distal lung parenchyma. Surfactant deficiency promotes atelectasis, typically characterized by low lung volumes and reduced lung compliance. Lung function is also reflective of the degree of structural maturation, as surfactant deficiency is predominantly a disease of the premature infant.

In the intubated infant, lung resistance measures are highly variable and not reproducible (22–32 %, ICC <0.75), in contrast with less variable and more reproducible measurements of lung compliance (obtained from esophageal manometry). Hence, the clinical relevance of dynamic mechanics measurements of resistance in intubated newborn infants with respiratory distress is questionable (Gappa et al. 2006a).

Measurements of impedance, obtained using forced oscillatory mechanics (a quasistatic lung mechanics measurement), may provide a more reliable assessment of lung mechanics. Dorkin measured respiratory impedance in six paralyzed and intubated infants, three of whom also had pulmonary interstitial emphysema (Dorkin et al. 1983). The tracheal tube contributed to almost all the inertance and approximately 50 % of the respiratory system resistance in the intubated infant. After subtraction of the impedance of the endotracheal tube, resistance ranged from 22 to 34 cm H₂O/L/s, compliance from 0.22 to 0.68 mL/cm H₂O, and inertance from 0.0056 to 0.047 cm H₂O/L/s (Gappa et al. 2006a; Dorkin et al. 1983).

The low-frequency forced oscillation technique (LFOT) evaluates impedance simultaneously across a range of frequencies (usually ~0.5–14 Hz). Fitting of the resultant impedance data to the constant-phase model permits estimation of partitioned mechanical variables of the airways and the parenchymal tissues (Hantos et al. 1992b). Using the LFOT, impedance measurements in naïve (surfactant-deficient) newborn preterm lambs showed that respiratory system resistance (R_{rs}) and reactance (X_{rs}) are markedly frequency dependent (Pillow et al. 2001a). Respiratory system resistance in the preterm infant is also dominated by the resistive properties of the tissues, contrasting sharply with the predominant airway contribution to respiratory

system resistance in later life (Pillow et al. 2005). Although compliance is also low (increased elastance), the tissue resistance is disproportionately greater, resulting in mechanical uncoupling of the parenchyma and increased hysteresivity (ratio of tissue resistance to tissue elastance) (Pillow et al. 2001a, 2005). Increased surfactant pool size (Pillow et al. 2004a) and lung volume recruitment (Pillow et al. 2004b) both enhance mechanical coupling of the tissues, evident as a lowering of the hysteresivity ratio in the lung. Increased contribution of the tissues to respiratory system mechanics, and the associated increased frequency dependence, results in elevation of the resonance frequency of the lung (Pillow et al. 2001a). Frequency dependence also becomes less marked with increasing postnatal age (Fig. 4.11) (Pillow et al. 2005).

Variability in measurements of lung mechanics in newborn infants in part reflects lung maturation associated with advancing gestation: lung compliance increases 0.17 mL/cm H₂O/week, to reach mean (SD) values of 2.50 (0.07) mL/cm H₂O at term equivalent (Bhutani et al. 2005). Other factors include in utero fetal exposures such as placental nutrition, inflammation, antenatal steroids, and postnatal treatments including caffeine, glucocorticoids, surfactant, and ventilation modality. Early treatment with caffeine in surfactant-treated immature baboons increased C_{rs} over the first day of life and increased ventilatory efficiency index (Yoder et al. 2005).

The initial benefit of antenatal steroids on improved lung compliance at birth fades beyond 1 week after initial exposure (McEvoy et al. 2008). There is no evidence of that antenatal steroids have a persistent effect on lung mechanics: infants born at term after exposure to up to three courses of betamethasone at gestations between 25 and 33 weeks had no difference in gas mixing or lung volume/mechanics when compared to nonexposed term controls (Hjalmarson and Sandberg 2011). Like antenatal steroids, postnatal steroids also increase respiratory system compliance (Durand et al. 1995). Low-dose and high-dose postnatal dexamethasone for CLD achieve a similar increase in C_{rs} suggesting equal effectiveness for improvement of lung volume

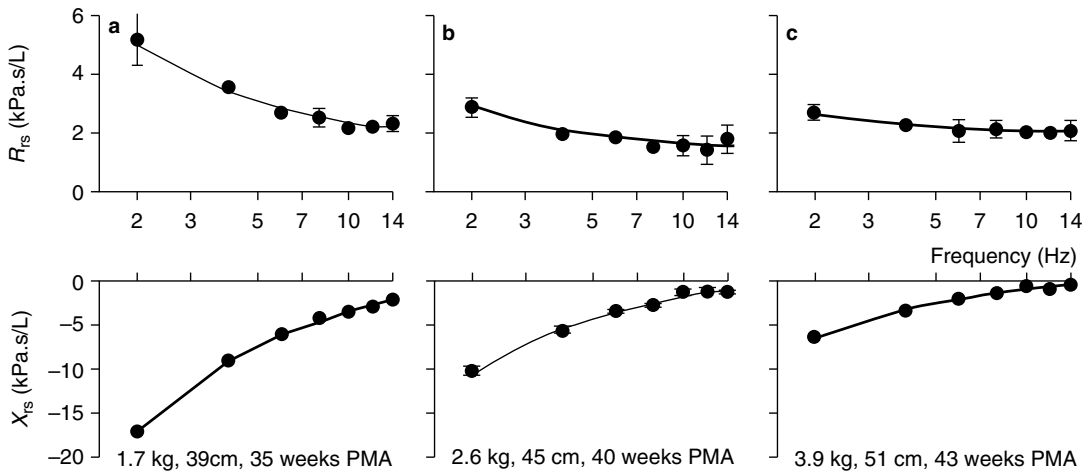


Fig. 4.11 Representative impedance spectra from two newborn infants: Panels **a** and **b** illustrate impedance spectra for a 32-week preterm infant at 35-week postmenstrual age (panel **a**) and on repeat measurement at 40-week PMA). Panel **c** shows the impedance spectra from a healthy term infant at 42-week postmenstrual age. Figure illustrates the alteration in respiratory impedance that occurs with postnatal maturation (**a**, **b**) and the marked frequency dependence of respiratory impedance in the

more immature infant (**a**). Solid lines indicate the fit of the constant-phase model. R_{rs} respiratory resistance (comprising frequency-dependent tissue resistance and frequency-independent airway resistance), X_{rs} respiratory reactance (incorporating tissue elastance and airway inductance), PMA postmenstrual age. Symbols and bars are mean (SD) values from technically acceptable measurements in the same infant (Adapted from Pillow et al. (2005))

(McEvoy et al. 2004). Early postnatal dexamethasone may be more effective than late dexamethasone in achieving lower R_{aw}/R_{rs} and higher specific conductance (sG_{aw}) (Merz et al. 1999; Vento et al. 2004), which may indicate a degree of fixed change in the airway walls in infants receiving delayed glucocorticoid treatment.

During administration, surfactant represents a fluid bolus in the airway that increases inspiratory and expiratory time constant, associated with an acute increase in respiratory system resistance. Effective delivery of surfactant to the lung thus benefits from a transient increase in the inspiratory time and potentially brief increase in the delta P (peak inspiratory pressure–positive end-expiratory pressure) to overcome the increase resistance resulting from the fluid bolus. Treatment with exogenous surfactant (da Silva et al. 1994) or increases in positive end-expiratory pressure (PEEP) during recruitment from atelectasis increases lung volume: (Dimitriou et al. 1999) lung volume increases by $61 \pm 39\%$ within a median of 4 min after surfactant administration, with altered distribution of lung volume towards

the dorsal rather than ventral compartment. The increase in lung volume after surfactant or volume recruitment maneuvers increases maximal compliance of the respiratory system, with higher tidal volumes achieved at lower pressures than required prior to treatment (Miedema et al. 2011a; McEvoy et al. 2010). Importantly, the increase in compliance also impacts on the time constant ($\tau = R_{rs} \times C_{rs}$) of the respiratory system. Changes in the inspiratory and expiratory time constants need to be monitored as they necessitate adjustment of the inspiratory and expiratory times and influence the maximal frequency that can be used during ventilation with passive expiration.

Compared to treatment of RDS with synchronized intermittent mandatory ventilation (SIMV), a small clinical trial showed that infants treated with high-frequency oscillatory ventilation (HFOV) have early and sustained improvement in pulmonary mechanics and higher dynamic respiratory compliance (Vento et al. 2005). The improvement in pulmonary mechanics in patients treated with HFOV is likely associated with enhanced lung volume recruitment.

The neonatal lung with RDS exhibits hysteresis (Miedema et al. 2011b). Hence lung recruitment maneuvers that aim to recruit the lung and subsequently ventilate it on the most compliant part of the deflation pressure volume curve can achieve effective ventilation with minimum pressure and volume cost of ventilation. Importantly, recruitment of the lung by increasing mean distending pressure during HFOV is also associated with changes in compliance and the time constant for volume delivery during HFOV (Pillow 2012). Consequently, volume delivery can vary substantially over the time course of an HFOV volume recruitment maneuver (Miedema et al. 2012) and potentially result in rapid fluxes of the partial pressure of arterial carbon dioxide. The effect of compliance on volume delivery during HFOV is more evident at lower frequencies (Pillow 2012; Pillow et al. 2001b). The development of HFOV ventilators that incorporate volume guarantee during HFOV will provide protection from such rapid changes in ventilation during HFOV.

Infants with RDS often have their clinical course complicated by the persistence of a patent ductus arteriosus (PDA), which presents as a left–right shunt. Ligation of a PDA (left–right shunt) increased dynamic compliance by 77 % in 16 newborn infants measured before and after ligation, but did not influence dynamic R_{rs} or mean airway pressure (Szymankiewicz et al. 2004a).

4.3.1.3 Meconium Aspiration Syndrome

Although meconium aspiration syndrome (MAS) is often considered as a high airway resistance disease due to the presence of meconium in the airways, studies in rabbits show that the acute aspiration of meconium also causes a significant reduction in the lung–thorax compliance (Sun et al. 1993). Impaired compliance after MAS is responsive to standard surfactant instillation (Sun et al. 1993). Larger volume (15 mL/kg) surfactant lung lavage is an emerging treatment for MAS: following surfactant lung lavage, dynamic compliance approximately doubled, and airway resistance nearly halved in a group of MAS infants on mechanical ventilation (Szymankiewicz et al. 2004b). These

changes in dynamic respiratory mechanics were associated with a decrease in mean (SD) airway pressure from 12.4 ± 3.6 to 5.4 ± 2.1 cm H₂O within 48 h after surfactant lung lavage.

Meconium appears to have a differential effect on hyperreactivity of the airways and the lung tissue. Whereas tracheal smooth muscle reactivity increases with increasing meconium concentration in response to histamine and acetylcholine, a negative correlation was observed in the lung tissue (Mokry et al. 2007). Airway hyperresponsiveness 2 weeks after birth (approximately 5 days after cessation of ECMO) is responsive to bronchodilator treatment (Koumbourlis et al. 1995) as evidenced by percent change in MEF₂₅ and the MEF₂₅/FVC ratio. Airway hyperreactivity after MAS is also reduced by budesonide (Mokry et al. 2007).

Limited information is available for the long-term lung function outcomes after MAS. Neonates treated with ECMO for meconium aspiration have better long-term lung function outcomes than infants with diaphragmatic hernia treated with ECMO in the neonatal period (Spoel et al. 2012a), most likely reflecting differences in lung capacity and structure. At least 50 % of children who had MAS in the neonatal period have evidence of trapped air on lung function during mid-late childhood. There are no published reports evaluating responsiveness to bronchodilators beyond infancy after neonatal MAS.

4.3.1.4 Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension of the newborn (PPHN) presents with profound hypoxia either in the absence of significant lung disease (primary PPHN) or hypoxia out of proportion with the degree of respiratory disease (secondary PPHN – complicating RDS, meconium aspiration, pneumonia, etc.). Lung function in 1-year-old infants who had PPHN and who were treated with inhaled nitric oxide (iNO) but not extracorporeal membrane oxygenation (ECMO) was compared with lung function outcomes of infants who were randomized to receive either ECMO or conventional management as part of the UK ECMO trial. $V'_{\max, FRC}$ was lower than predicted in

Table 4.1 Longitudinal results of spirometry after neonatal ECMO after bronchodilation

Age (year)	5		8		12	
Subjects, <i>n</i>	72		77		42	
Bronchodilation	Pre	Post	Pre	Post	Pre	Post
SDS FEV ₁						
MAS	−0.16 (−0.51, 0.19)	0.49 (0.16, 0.82)**	−0.49 (−0.77, −0.22)*	0.12 (−0.16, 0.40)	−0.69 (−1.1, −0.28)*	0.01 (−0.45, 0.24)
CDH	−1.7 (−2.3, −1.2)*	0.01 (−0.53, 0.47)	−2.5 (−3.0, −2.0)*	−2.3 (−3.0, −1.5)***	−3.2 (−4.4, −2.6)*	−2.7 (−3.9, −1.5)*

Adapted with permission from Spoel et al. (2012a)

Mean (95 % CI) standard deviation score (SDS) show for FEV₁ (forced expiratory volume in 1 s). Number of patients studied in each group: meconium aspiration syndrome (MAS) – 35, 46, and 26 at 5 years, 8 years, and 12 years; congenital diaphragmatic hernia (CDH) – 15, 14, and 5 at 5 years, 8 years, and 12 years. SDS significantly below normal (SDS=0; one sample *t*-test): **p*<0.05; ***p*<0.01; ****p*<0.001

all three groups (*p*<0.001). There were no statistical differences between the three groups in the Z-scores for $V'_{\max, \text{FRC}}$ (Hoskote et al. 2008). Nonetheless, only 26 % of iNO-treated infants had $V'_{\max, \text{FRC}}$ Z-scores below normal compared to 37 and 56 %, respectively, for ECMO and CM groups. A prospective evaluation of lung function in infants with PPHN treated with/without iNO was reported by Dobyns and colleagues (1999): compared to healthy control infants of the same age, there were no differences in lung volume or passive respiratory mechanics for infants with PPHN, nor was there any effect of iNO on later pulmonary function in the PPHN group. Together, these results suggest that iNO treatment does not worsen outcome compared to ECMO or conventional management.

4.3.1.5 Congenital Diaphragmatic Hernia

Infants with congenital diaphragmatic hernia have impaired airway function in the first year of life: maximal expiratory flows at FRC were a mean Z-score of −1.5 lower than healthy term infants (i.e., 1.5 standard deviations below the mean FRC for healthy term infants) with no evidence of significant change between 6 and 12 months of age (Spoel et al. 2012b). Conversely, and perhaps surprisingly, given the usual association of CDH with pulmonary hypoplasia in at least one lung, Spoel noted that measured values of functional residual capacity were relatively high (47 % fell above the normal range) (Spoel et al. 2012b). As expected, mean Z-score for FEV₁ and FVC was negatively

influenced by the presence of chronic lung disease, the duration of ventilation, and ECMO support (Spoel et al. 2012a). Patients with CDH develop hyperinflation, with elevated plethysmographic FRC at 1 year (Hofhuis et al. 2011) that is still evident at 8–12 years (Spoel et al. 2012a; Hamutcu et al. 2004; Majaesic et al. 2007).

Spoel showed that greater impairment was evident in infants with CDH who required extracorporeal membrane oxygenation (Spoel et al. 2012b). However, poorer outcome in ECMO-treated CDH may reflect the initial severity of disease rather than ECMO: Beardsmore showed that ECMO per se did not worsen respiratory function at 1 year of age compared to conventionally ventilated controls (Beardsmore et al. 2000).

Spoel and colleagues also noted deterioration in lung function over time (5–12 years) in patients with CDH who were treated with ECMO in the neonatal period (see Table 4.1) (Spoel et al. 2012a): mean (SE) SDS score for FEV₁ after bronchodilation was higher at 5 years (−0.71 (0.40)) than at 8 years (−2.27 (0.36)) and 12 years (−2.73 (0.61)). Deterioration over time may be related to maldevelopment of the alveoli and pulmonary vessels with disturbed lung growth. It is also possible that increased susceptibility to recurrent respiratory tract infections may contribute to deterioration in lung function over time. An active lifestyle and healthy eating pattern may be especially important for children with CDH to counteract the deterioration in lung function over time, given the known positive effect of participation in sports and the negative interaction of

BMI with exercise capacity (van der Cammen-van Zijp et al. 2011). Similarly, it may be especially important to treat recurrent infections of the respiratory tract and actively manage asthma to avoid limitation of exercise capacity and deterioration of lung function. Prolonged follow-up of children with CDH is warranted.

4.3.2 Chronic Neonatal Lung Disease

4.3.2.1 Bronchopulmonary Dysplasia

BPD is most commonly considered as the chronic respiratory condition complicating extreme prematurity and/or prolonged neonatal mechanical ventilation. Factors that independently influence the tidal flow–volume-derived indices include variations in disease severity, degree of alteration to airway and lung mechanics, and also the requirement for oxygen supplementation (Baldwin et al. 2006). There are, nonetheless, quantitative differences in tidal breathing function measured in BPD infants when compared with measurements obtained from healthy term and preterm controls. BPD infants are consistently more tachypneic than their healthy counterparts (Baldwin et al. 2006), but differences in other lung function variables are less consistent. Tidal volume (V_T) is either less than (Paetow et al. 1999) or similar to (Patzak et al. 1999; Schmalisch et al. 2003) values obtained in healthy infants: V_T relative to healthy infants may also decrease with advancing postnatal age (Tepper et al. 1986b), likely reflecting the altered maturational progression in lung structure and function. BPD infants have increased minute ventilation (MV). Increased MV is primarily due to increased respiratory rate rather than increases in V , in part reflecting increased dead space ventilation.

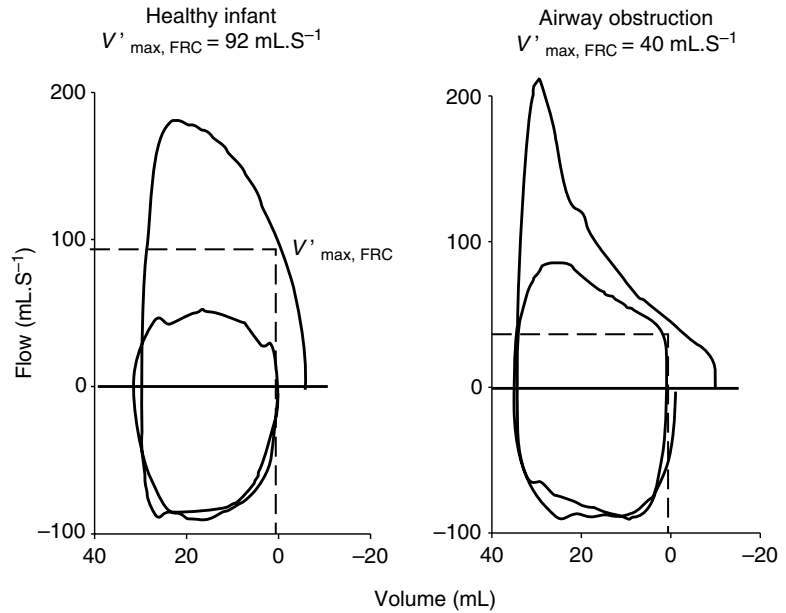
Infants with BPD have an increased work of breathing. Within the tidal flow–volume loop, increased work of breathing is evident from linear or concave expiratory limb morphology. BPD infants also have a less variable shape to the tidal flow–volume waveform, indicating that they are functioning near their maximum respiratory capability with minimal reserve capacity

to adapt to changes in intrinsic (e.g., airway obstruction, infection, or aspiration) or extrinsic (e.g., cold stress) environment (Baldwin et al. 2006). Tidal flow indices are difficult to interpret in part due to opposing effects of neurorespiratory control and lung mechanics on the morphology of the tidal flow waveform. Whereas BPD infants have higher respiratory drive (quantified from the mean inspiratory flow: V_T/t_I where t_I is inspiratory time), the ratio of the time to peak expiratory flow relative to expiratory time ($t_{PEF}:t_E$) after methacholine-induced airway obstruction can either increase or decrease (Clarke et al. 1994). Normal fluctuations in V_T , t_I , and MV seen in healthy infants in response to alternate hypoxic–normoxic breath testing are not evident in BPD infants, indicating reduced chemoreceptor sensitivity to hypoxic stimulus (Calder et al. 1994).

Lung and chest wall mechanics of infants with bronchopulmonary dysplasia (BPD) were extensively reviewed by Gappa and colleagues (2006b). Changes are reflective of maldevelopment of the lungs and airways and remodelling of the lung parenchyma and airway walls associated with increased collagen content. In preterm infants, respiratory system compliance (C_{rs}) increases relative to body weight over the first 2 years of life, while an initially high respiratory system resistance (R_{rs}) decreases over the same period (Baraldi et al. 1997a). Airway walls of preterm infants are more compliant than term infants as evidenced through measurements obtained using the high-speed interrupter technique (HIT) (Henschen et al. 2006).

Following the NICHD consensus conference in 2001 (Jobe and Bancalari 2001), some investigators evaluated differences in lung function according to whether infants had mild, moderate, or severe chronic lung disease. Using the single occlusion technique, Hjalmarson and Sandberg showed that infants with severe bronchopulmonary dysplasia (born at mean 25 weeks GA) had increased specific conductance and decreased specific compliance (sC_{rs}) compared to healthy preterm infants (born at mean 29 weeks gestation) (Hjalmarson and Sandberg 2005). There were no differences in lung mechanics between

Fig. 4.12 Representative flow–volume curves obtained during rapid thoracic compression from healthy (left) and flow-obstructed (right) infants. The descending portion of the expiratory flow–volume curve in the flow-obstructed infant has a characteristic concave (to the x-axis) shape. Dashed line indicated point at which $V'_{\max, \text{FRC}}$ was determined (Adapted with permission from Lum et al. (2006b))



the healthy preterm infants and those with mild or moderate bronchopulmonary dysplasia. The data published by Tortorolo et al. indicate a similar trend towards lower C_{rs} at day 7 in infants who later went on to develop mild BPD and to a greater extent in severe BPD (Tortorolo et al. 2002). Their results contrast with the findings by Shao and colleagues in infants of similar gestations that infants with BPD had decreased C_{rs} (10.8 vs 16.0 mL/kPa/Kg), but no difference in specific sC_{rs} (0.69 vs 0.75 mL/kPa/kg) or R_{rs} (6.6 vs 7.3 cm H₂O/mL/s) compared to non-ventilated preterm infants. Infants with BPD do not show an improvement in airway resistance (R_{aw} , measured by plethysmography) over a 4-month period (Shao et al. 1998).

Several authors have attempted to use lung function as a predictor of BPD. The value of initial R_{rs} for prediction of lung disease is unclear: some have found increased initial R_{rs} is associated with respiratory outcome at 1 year (Choukroun et al. 2003; Lui et al. 2000; Snepvangers et al. 2004), whereas others observed that R_{rs} is not predictive of BPD (Tortorolo et al. 2002). Both Lui (Lui et al. 2000) and Merth (Merth et al. 1997) showed that early RDS is not an important determinant of later lung function. Serial measurements of compliance, however, show that lower C_{rs} values after

day 5 were evident in infants who later developed severe BPD. Merth observed that BPD infants have reduced C_{rs} at 1 year of age irrespective of RDS (Merth et al. 1997).

$V'_{\max, \text{FRC}}$ obtained using the tidal rapid thoracic compression technique is reported consistently as being lower than healthy controls throughout the first 3 years of life, regardless of the BPD era or treatment strategies (Lum et al. 2006b). Reduced expiratory flows are indicative of abnormal structural and functional development of the airways (Fig. 4.12). Serial lung function measurements in infants with both BPD and “healthy” unsedated preterm infants indicate a decline over the first year of life, suggesting that factors other than BPD may contribute to abnormal airway function in preterm infants (Hoo et al. 2002b). Raised volume rapid thoracic compression (RVRTC) measurements show similar mild–moderately severe airflow obstruction. However the predominance of airflow obstruction primarily at low lung volumes indicates the pathology is more likely to involve the small peripheral rather than larger central airways (Lum et al. 2006b). Concurrent increased residual volume (RV), FRC, and RV/TLC (total lung capacity) ratios were more marked in infants with recurrent wheeze, indicative of a degree of hyperinflation and gas trapping.

Intermediate values (between healthy controls and wheezy BPD infants) were observed for RV, FRC, and RV/TLC in non-wheezy preterm infants (Robin et al. 2004), likely reflective of abnormal airway growth or the effects of preterm delivery. Forced deflation from FRC showed that preterm infants with developing BPD have severe lower airway obstruction as early as 3–4 weeks postnatal age. Increased flows and FVC following bronchodilation indicate that reopening of obstructed airways is achieved with bronchodilators (Motoyama et al. 1987).

A recent systematic review and meta-analysis assessed the effect of preterm birth on later FEV₁; (Kotecha et al. 2013) 59 studies were included in the meta-analysis, including 28 studies in children born preterm without BPD and 39 studies in children with BPD diagnosed at either 28 day of life (BPD₂₈) or 36 weeks postmenstrual age (BPD₃₆). The meta-analysis showed that just being born preterm decreased FEV₁ compared to term-born controls, with further decrements in FEV₁ evident for the BPD₂₈ and BPD₃₆ week groups. The mean differences (95 % CI) for % FEV₁ compared with term-born controls were −7.2 % (−8.7 %, −5.6 %) for preterm group without BPD and −16.2 % (−19.9 to −12.4 %) and −18.9 % (−21.1 to −16.7 %) for the BPD₂₈ and BPD₃₆ groups, respectively. Including data from preterm studies not including a control group resulted in a pooled % FEV₁ estimate of 91.0 % (88.8–93.1 %) for preterm infants without BPD, 83.7 % (80.2–87.2 %) for BPD₂₈, and 79.1 % (76.9–81.3 %) for BPD₃₆, respectively. Of interest, the authors noted that %FEV₁ for BPD₂₈ has improved over the years. BPD survivors also have lower forced expiratory flows: 70 % of children with BPD had maximal flow at functional respiratory capacity ($V_{\max}$ FRC) below 40 % of the predicted value (Baraldi et al. 1997a). Forced expiratory flow at 25 % of forced vital capacity (FEF_{25–75}) was reduced in young adolescents born prematurely, regardless of prior BPD or level of respiratory support (Anand et al. 2003). Of concern, Doyle and colleagues showed that airflow limitation worsened between 8 and 18 years (Doyle et al. 2006). Together, these data suggest that the preterm infant population is at risk of developing chronic obstructive disease and should

receive long-term respiratory follow-up (Baraldi and Filippone 2007a; Filippone et al. 2003; Lum et al. 2011). Airway obstruction is accompanied by impaired diffusing capacity in children and adults born prematurely (Hakulinen et al. 1996; Vrijlandt et al. 2006). Similar findings in infants and toddlers with BPD in the face of normal alveolar volumes indicate parenchymal disease and impaired alveolarization (Balinotti et al. 2010).

4.3.2.2 Bronchial Hyperresponsiveness

Several studies have evaluated the effect of bronchodilators on lung mechanics in infants with BPD. Bronchodilators decrease R_{rs} , without affecting C_{rs} ; ultrasonic nebulizers appear to be most effective (Fok et al. 1998).

Bronchial hyperresponsiveness at 2 years of age was related to mean neonatal C_{rs} and R_{rs} over the first 3 days in ventilated preterm neonates using breath occlusion test. C_{rs} but not R_{rs} was related to bronchial hyperresponsiveness at 2 years' age (Snepvangers et al. 2004). Fifty-six percent of children in the Epicure study born at 25 weeks PMA or less had abnormal baseline spirometry at 11 years of age, with 27 % showing a positive bronchodilator response: more marked responses were evident in the infants with prior BPD (Fawke et al. 2010). Less than half of the Epicure study children with abnormal lung function at 11 years were receiving treatment, suggesting more targeted respiratory follow-up is warranted. The published literature on persistence of bronchial hyperreactivity into early adulthood in the population of young adults born prior to routine antenatal glucocorticoid and postnatal surfactant treatment is conflicting: both persistence (Halvorsen et al. 2004) and resolution (Narang et al. 2008) of bronchial hyperresponsiveness are reported, although both studies report persistently abnormal baseline spirometry.

Essentials to Remember

- Measurements of dynamic mechanics are most often obtained in intubated infants, but measurements of dynamic resistance are highly variable and may

not be reliable. Reasons for variability include the highly frequency-dependent nature of respiratory mechanics, rapidly changing nature of respiratory disease, maturation and the acute effects of antenatal exposures, and postnatal treatments and interventions.

- RDS is typically characterized by low lung volumes, reduced lung compliance, and elevated tissue resistance.
- Meconium aspiration is characterized by both increased resistance and decreased compliance. Both resistance and compliance are improved by surfactant lavage. MAS may be complicated by airway hyperreactivity and gas trapping beyond infancy.
- Infants with congenital diaphragmatic hernia have impaired airway function at 1 year of age, with evidence of continuing deterioration throughout childhood. Worse lung function is likely associated with initial severity of disease and intensity/duration of mechanical ventilation.
- BPD infants are typically more tachypneic than their healthy counterparts and have increased work of breathing. Airway walls are more compliant and may be prone to collapse. While lung function outcomes for infants with BPD have improved over the last one to two decades, airflow limitation remains an issue for long-term respiratory function after bronchopulmonary dysplasia and may worsen with time. Diffusing capacity is also impaired in children and adults born prematurely and may reflect parenchymal disease and impaired alveolarization.
- Although patients receiving ECMO generally have worse lung function than those treated without ECMO, this is likely due to the initial severity of lung disease and duration of mechanical ventilation rather than an effect of ECMO on long-term lung function per se.

Persistence of bronchial hyperreactivity into adulthood is unknown for the current population of premature infants.

Educational Aim

To describe flow (F), lung volumes (V), and respiratory pressure (P) measurements together with resistance (R) and compliance (C) measurements in restrictive lung diseases, obstructive lung diseases, and neuromuscular disorders (NMD)

4.4 Respiratory Mechanics in Pediatric Diseases

Véronique Nève and Francis Leclerc

4.4.1 Restrictive Lung Disease

A restrictive ventilatory defect is observed when expansion of the lung is restricted because of alterations in lung parenchyma or as a consequence of extraparenchymal diseases affecting pleura, chest wall, or neuromuscular apparatus.

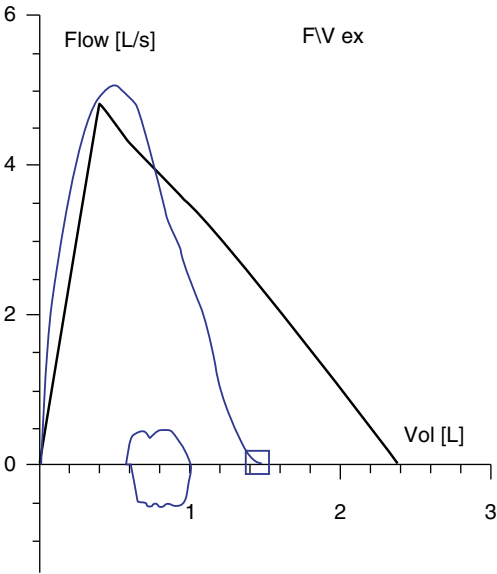
4.4.1.1 Restrictive Ventilatory Defect of Pulmonary Origin

4.4.1.1.1 Chronic ILD

Chronic ILD are characterized by derangements of the alveolar walls and loss of functional alveolar–capillary units. Pediatric ILD comprises a heterogeneous group of rare disorders with considerable mortality (Clement 2004; Fan et al. 2004; Fan and Langston 1993). Chronic ILD in immune-competent children has been defined as the presence of respiratory symptoms and/or diffuse infiltrates on chest radiographs, abnormal pulmonary function tests (PFT) with evidence of restrictive ventilatory defect and/or impaired gas exchange, and persistence of any of these findings for >3 months (Clement 2004). PFT, in children over 6 years, show a reduced forced VC (FVC) and FEV₁ and a normal or elevated FEV₁/FVC ratio (Fan et al. 2004) (Fig. 4.13). The

Fig. 4.13 In chronic interstitial lung disease, pulmonary function tests, in children over 6 years, show a reduced forced vital capacity (FVC) and FEV₁ and a normal or elevated FEV₁/FVC ratio and a restrictive ventilatory defect with decreased total lung capacity (TLC)

		Pre	Pred	% Pred
VC	[L]	1.51	2.47	61
ERV	[L]	0.49	0.81	61
VT	[L]	0.45	0.42	106
ITGV	[L]	1.14	1.63	70
RV	[L]	0.65	0.85	77
TLC	[L]	2.16	3.32	65
RV % TLC	[%]	30.12	24.96	121
FVC	[L]	1.46	2.47	61
FEV 1	[L]	1.41	0.81	69
FEV 1 % VC MAX	[%]	93.06	24.96	110



decrease in TLC, in general, is relatively less than that of VC because of normal chest wall recoil and inspiratory muscle function in most patients (Martinez and Flaherty 2006).

Functional residual capacity (FRC) and residual volume (RV) are normal or elevated resulting in increased FRC/TLC and RV/TLC (Gaultier et al. 1980; Steinkamp et al. 1990; Zapletal et al. 1985). The latter finding suggests air trapping (Fan et al. 2004). Airflow limitation has been demonstrated in some studies (Fan and Langston 1993). Diffusing capacity of carbon monoxide (DL_{CO}), that evaluates the capacity of the lung to exchange gas across the alveolar capillary interface, is low in absolute term but normal when corrected for alveolar V (Gaultier et al. 1980; Zapletal et al. 1985).

The lung P/V curve is shifted down, and elastic recoil P at maximum inspiration is increased (Fan and Langston 1993; Steinkamp et al. 1990; Zapletal et al. 1985). Reduced C_L is observed, with lower specific C_L in children with fibrotic changes on transbronchial lung biopsy specimen (Steinkamp et al. 1990).

The decreased C_L and increased elastic recoil can increase the retractive force exerted on the walls of lung airways and reduce the airway R (R_{aw}) or increase FEV₁% and preserve the peak expiratory F (PEF). However, once lung V becomes severely reduced, PEF declines because it is then measured at a relatively small lung V (Cotes et al. 2006).

PFT can aid in establishing disease severity and prognosis. In nonspecific interstitial pneu-

monia and idiopathic fibrosis, $DL_{CO} < 40\%$ corresponds to advanced disease and predicts impaired survival. Similarly, exertional desaturation $< 88\%$ at baseline testing and a decrease in FVC $> 10\%$ over the course of the short-term follow-up identify patients at particular risk of mortality (Martinez and Flaherty 2006).

4.4.1.1.2 ALI/ARDS

ALI/ARDS are characterized by an acute onset of respiratory failure, diffuse bilateral pulmonary infiltrates on the chest radiograph, the absence of clinical evidence of left atrial hypertension, and a ratio of PaO_2 to FiO_2 (P/F) of less than 200 mmHg (regardless of PEEP). Acute lung injury (ALI) is a subset of ARDS with less severe impairment in oxygenation ($P/F < 300$) (Bernard et al. 1994). SpO_2/FiO_2 (S/F) may be a good noninvasive surrogate marker for P/F in children: S/F ratios of 263 and 201 have been shown to correspond to P/F ratios of 300 and 200, respectively, the ARDS cut-off of 201 having 84 % sensitivity and 78 % specificity (Bach and Bianchi 2003). Decreased C_L was associated to these items (Ware and Matthay 2000). ALI/ARDS are rare diseases in children and have mortality rates ranging from 18 to 75 % (Flori et al. 2005; Zimmerman et al. 2009). Mechanical ventilation represents the main therapeutic support to maintain acceptable pulmonary gas exchange while treating the underlying disease. A “lung protective ventilation strategy” with limitation in airway P and tidal volume (VT) (The Acute Respiratory Distress Syndrome Network 2000) led, in adult studies, to a reduction in mortality at day 28 and a reduction in hospital mortality (Petrucci and Iacovelli 2007; The Acute Respiratory Distress Syndrome Network 2000). No published data exist for children, but practice in PICU is derived from adult patients (Khemani and Newth 2010).

4.4.1.1.2.1 Acute Phase

The most characteristic alteration in acute ARDS lung is marked fall in C_L caused by loss of surfactant function, atelectatic lung regions, accumulation of interstitial/alveolar plasma leakage (Ware and Matthay 2000), and an associated fall in FRC (Hammer 2001). In adults, the decrease in C_L was shown to be more important in early ARDS from pulmonary origin (and associated with normal

chest wall C (C_{cw})) than in extrapulmonary ARDS. The latter was associated with low C_{cw} (Gattinoni et al. 1998). A decrease in respiratory system compliance (C_{rs}) and a proportional decrease in TLC, FVC, and FRC were also observed in children during the acute phase of ARDS (Hammer et al. 1998; Newth et al. 1997).

ALI/ARDS may resolve completely in some patients, while in others it progresses to fibrosing alveolitis with persistent hypoxemia and a further decrease in C_L (Ware and Matthay 2000). Fibroproliferation occurs early in ARDS, and its extent may be predictive of outcome (Marshall et al. 2000). The recovery phase is characterized by the gradual resolution of hypoxemia and improved C_L (Ware and Matthay 2000). Pharmacologic interventions, such as corticosteroids, starting in the late course of ARDS may reduce fibrosis and may have a beneficial impact on pulmonary outcome (Tang et al. 2009).

4.4.1.1.2.2 Long-Term Sequelae

Several studies have demonstrated persistent impairment in pulmonary function of unknown long-term significance for children who required mechanical ventilation in pediatric intensive care units for respiratory failure (Khemani and Newth 2010). Most survivors of ARDS have persistent mild reductions of DL_{CO} even as long as a year after their episode. The lung V and F return to normal in most instances, although a subset of patients will have persistent impairment. Both obstructive and restrictive deficits may be seen (Alberts et al. 1983; Elliott et al. 1981; Ghio et al. 1989; Hert and Albert 1994; Peters et al. 1989).

Timing of recovery occurring in the first year after ARDS was described in two prospective studies of adult survivors of ARDS (Herridge et al. 2003; McHugh et al. 1994). After discharge from the ICU, a restrictive ventilatory defect and reduced DL_{CO} were observed in almost all patients and an obstructive defect in only 5 %. Improvement was observed until 6 months after discharge. A relatively static period was observed after that. By 6 months, abnormalities in FVC, TLC, and DL_{CO} were observed in 55, 45, and 26 %, respectively, of patients. Patients with more severe ARDS, as determined by their higher ALI scores (corresponding to patients ventilated

for >2 weeks), were more impaired for FVC throughout the follow-up and did not return to normal pulmonary function levels (McHugh et al. 1994). Patients of Herridge's study were shown to have a mild restrictive defect with mild to moderate reduction in DL_{CO} at 3 months. Lung V and spirometric measurements were normal by 6 months, but DL_{CO} remained low throughout the 12-month follow-up (Herridge et al. 2003).

For the pediatric age group, a few small-sized observational cohort studies have reported sequelae in 10–100 %, in mostly asymptomatic subjects (Ben-Abraham et al. 2002; Fanconi et al. 1985; Golder et al. 1998; Lyrene and Truog 1981; Weiss et al. 1996). Obstructive (reversible and nonreversible airflow obstruction) and restrictive abnormalities have been observed after discharge. Like in adults, recovery during the following months reached plateau levels at 12 months with no further improvement (Golder et al. 1998).

Decrease in C_L was shown to persist in ≥ 50 % of children and adults, evaluated 1–2 months (Aggarwal et al. 2000), or 34 months after ARDS (Klein et al. 1976), and was associated with a restrictive defect in some patients. Symptomatic upper airway obstruction as a result of laryngotracheal injury from long-term intubation has been described in minority (10 %) of adults after ARDS with evidence of upper airway obstruction on inspiratory and expiratory F/V curves (Elliott et al. 1988).

4.4.1.2 Restrictive Defect Arising in the Chest Wall

4.4.1.2.1 Obesity

The prevalence of childhood obesity is increasing in developed countries. Obese children have more respiratory symptoms than their normal-weighted peers, and respiratory-related disorders increase with increasing weight. The prevalence of asthma has also increased in children. Both obesity and asthma have their beginnings in early childhood (Litonjua and Gold 2008). Wheezing, asthma, and obesity seem to be associated (Guerra et al. 2002; Hancox et al. 2005; Schachter et al. 2001). However, three large studies (Bibi et al. 2004; Schachter et al. 2003; Wickens et al. 2005) showed a clear increase in symptoms of asthma in association with obesity but not more frequent

airway hyperresponsiveness in obese children (Deane and Thomson 2006).

C_{CW} is reduced in obesity, because of increased adiposity in the abdomen and around the thoracic cage that restricts rib expansion and because the decreased total thoracic and pulmonary V may pull the chest wall below its resting level to a flatten portion of its P/V curve. C_{CW} decrease correlated with CO_2 retention, independent of body fat, and with shortness of breath (Subramanian and Strohl 2004). C_L may be decreased in some obese individuals because of a large pulmonary blood volume and intrinsic alterations of elastic characteristics of lung tissues (Subramanian and Strohl 2004).

As additional fat in the abdomen raises the diaphragm, the FRC and expiratory reserve volume (ERV) are reduced in the erected position and further reduced in the supine position (Koenig 2001). The lung bases are poorly ventilated which contributes to hypoxemia. TLC and VC may also be reduced, but RV is usually maintained (therefore RV/TLC ratio may be increased). In morbidly obese individuals, an increase in body mass correlates with reduced FEV_1 (Carey et al. 1999) and FVC (FEV_1 /FVC ratio remains normal) (Zerah et al. 1993).

Data in children and adolescents confirm the reduced FRC and static lung V (Li et al. 2003) and the decrease in FVC and FEV_1 with increasing proportions of body fat as a percentage of body weight (Lazarus et al. 1997).

All these effects were shown to be reversible in morbidly obese patients (with body mass index (BMI) >40) following weight loss (Camargo et al. 1999; Carey et al. 1999; Deane and Thomson 2006).

In seated patients with simple morbid obesity, inspiratory and expiratory muscle strength is normal (Yap et al. 1995). When patients are supine, maximal inspiratory P (PI_{max}) decreases by about half as a result of overstretching of the diaphragm, causing it to operate on the descending limb of its length–tension curve (Laghi and Tobin 2003).

Morbidly obese patients without hypoventilation (simple obesity) compensate for the respiratory load by increasing respiratory drive and diaphragmatic pressure output (Pankow et al. 1998) and increasing rib cage contribution to tidal breathing.

4.4.1.2.2 Scoliosis

Scoliosis is the most common abnormality of the spine with direct effect on the thoracic cage. Idiopathic scoliosis (including infantile, juvenile, and adolescent) accounts for 80–85 % of scoliosis. Neuromuscular scoliosis (as in Duchenne muscular dystrophy (DMD) or spinal muscular atrophy (SMA)) and scoliosis associated with congenital vertebral abnormalities account each for 5 % of scoliosis. Infantile and congenital scoliosis, untreated, results in severe spinal deformities and is at risk of cardiopulmonary insufficiency before adulthood (Canet and Bureau 1990).

Patients with scoliosis and a Cobb angle $<70^\circ$ are usually asymptomatic, those with an angle between 70° and 100° often experience dyspnea on exertion, and those with the angle $>100^\circ$ are at risk for chronic respiratory failure (Estenne et al. 1998).

Scoliosis can produce severe reductions in lung V and restrictive ventilatory defect with decrease in FVC, FEV_1 , and TLC as well as a normal FEV_1/FVC ratio (Gagnon et al. 1989; Muirhead and Conner 1985; Upadhyay et al. 1993; Weber et al. 1975). Among patients with moderate to severe scoliosis (35 – 100°), the VC decrease is related to the Cobb angle. When the Cobb angle exceeds 100° (severe scoliosis), VC falls to about 50 % of predicted (Laghi and Tobin 2003). Impaired lung growth (Davies and Reid 1971), significant decrease in C_L and C_{CW} (at about 25–50 % of predicted in children and adults with scoliosis) (Laghi and Tobin 2003), and/or impaired muscle strength as a consequence of inefficient coupling between the respiratory muscles and the thoracic cage account for the effect of scoliosis on lung function. In adults with scoliosis and Cobb angles of 66 – 136° , P_{Imax} was about 50–76 % (Estenne et al. 1998; Laghi and Tobin 2003).

Decreased TLC is often associated with increased RV resulting in very high RV/TLC ratio (Day et al. 1994), probably reflecting the dysfunction of expiratory muscles, which do not allow full exhalation.

Significant gas trapping with elevated plethysmographic FRC/helium FRC ratio can occur with response to bronchodilators, indicating airway hyperresponsiveness that results from chronic

airway inflammation secondary to the poor clearance of secretions (Boyer et al. 1996). The chest distortion causes airway distortion thereby contributing to a slight increase in airway R (R_{aw}) (Canet and Bureau 1990). Scoliosis, by inducing significant displacement/rotation of the intrathoracic trachea and/or main stem bronchi, can cause mechanical obstruction as shown on the F/V loop with flattening of the initial portion of the expiratory loop suggesting central airway obstruction (Borowitz et al. 2001).

The decreased C_{rs} may account for the increased work of breathing, with increased transdiaphragmatic pressure during tidal breathing; increased rib cage contribution to tidal breathing; transversus abdominis recruitment during exhalation, as observed in most patients with severe scoliosis (Laghi and Tobin 2003); and the associated increased risk of respiratory muscle fatigue and eventual respiratory failure.

4.4.1.2.2.1 Neuromuscular Scoliosis

In contrast to idiopathic scoliosis which tends to stabilize (or progress at a lower rate) after the person reaches skeletal maturity, neuromuscular scoliosis (such as in DMD or SMA) continues to worsen because of the progressive worsening of the muscle weakness. Recurrent aspiration and pneumonias secondary to impaired clearance of airway secretions are potential complications. Due to the severity of their primary muscle weakness, patients with neuromuscular scoliosis may not be able to maintain adequate ventilation and may develop severe atelectasis (Koumbourlis 2006).

Scoliosis is reported in 60–100 % of SMA children and is due to the inability of the trunk muscles to support spine in the upright position. All children with type 2 SMA develop scoliosis starting from around 3 years. The average curve is more than 54° at 10 years of age (Mullender et al. 2008). As the scoliosis progresses, respiratory function deteriorates, and the risk of life-threatening complications increases (Rodillo et al. 1989). Spinal fusion is recommended when scoliosis progresses and reaches a Cobb angle of between 40° and 60° in children ≥ 10 years of age (Tsirikos and Baker 2006).

In DMD, scoliosis incidence ranges from 75 to 95 % (Muntoni et al. 2006). DMD develop

scoliosis after losing independent ambulation (in the second decade of life). Once scoliosis reaches 30° , it progresses with age and growth. Corticosteroids may delay the development and progression of scoliosis in DMD (Muntoni et al. 2006). Optimal timing for surgical intervention is while lung function is satisfactory and before cardiomyopathy becomes severe enough to risk arrhythmia under anesthesia (Cobb angle between 30° and 50°). Best prognosis for recovery seems to be $FVC > 40\%$, although others use the absolute VC of < 1.9 L as an indicator of rapid progression of scoliosis and poor prognosis (Finder et al. 2004). Comparison between pre- and postoperative pulmonary function reveals no improvement due to correction of scoliosis. Long-term studies show that decline of pulmonary function in DMD patients is unchanged in operated patients compared to patients who had no surgery (Muntoni et al. 2006).

4.4.2 Obstructive Lung Disease

4.4.2.1 Childhood Asthma and Wheezing Disorders

Asthma is the most frequent chronic disease observed in children (prevalence ranging from 8 to 12 % (ISAAC 1998)). Asthma is difficult to diagnose in children ≤ 5 years. Children presenting with wheeze at an early age belong to a heterogeneous group: early transient, late onset, and persistent wheezers (Martinez and Helms 1998). Half of the “early” wheezing children become asymptomatic by school age. They may have diminished lung function early on, but by 6 years lung function is improved (Martinez et al. 1995). Children who had wheezing that began in infancy and continued at 6 years demonstrated normal pulmonary function initially with reduced lung function by 6 years. Those children with “persistent wheezing” have some ongoing chronic inflammatory process that results in airway alterations and some loss of lung function in early childhood, which extends to varying degrees in adulthood (Oswald et al. 1997).

Respiratory syncytial virus (RSV) bronchiolitis in infancy is often associated with recurrent

wheezing and asthma during subsequent years. However, wheezing tends to diminish by school age or adolescence. Most follow-up studies of RSV bronchiolitis in infancy show that forced expiratory flow (FEF) rates and FEV_1 are lower at school age compared with control groups (Hall et al. 1984; Pullan and Hey 1982). Children who had been hospitalized for RSV bronchiolitis as infants later had lung function abnormalities similar to those found in children with asthma (Kattan et al. 1977; Wennergren and Kristjansson 2001).

Increased R to airflow is the basis of the clinical manifestations of asthma, including dyspnea and wheeze. Usually, airflow limitation is reversible. Fixed airway obstruction may be seen in later disease stage (Strachan et al. 1996) or be a component of a specific asthma phenotype (Bush 2004). Airway obstruction in childhood is associated with a reduced FEV_1 in adulthood (Jenkins et al. 1994; Roorda et al. 1994).

Airflow obstruction (AFO) can be assessed by body plethysmography, spirometry, forced oscillation technique (FOT), and interrupter technique, but these are more difficult to perform in children < 6 years. Incentive spirometry can be performed in the majority of children ≥ 3 years (Beydon et al. 2007b) together with FRC helium measurement and R measurement (using interrupter technique (R_{int})) (Beydon et al. 2007b), FOT, or plethysmography for measurement specific R_{aw} (sR_{aw}) (Dab and Alexander 1976). Infant PFTs are mainly research tools.

4.4.2.1.1 Forced Expiratory Volumes (FEV) and F/V Curves

The FEV_1 is the “gold standard” of measuring airway obstruction in children over 6 years (Miller et al. 2005; Pellegrino et al. 2005). Preschoolers often do not exhale for more than 1 s. Therefore FEV_1 may not be an accurate index of bronchial obstruction in this age group, and the utility of $FEV_{0.5}$ or $FEV_{0.75}$ as outcome measure in this age group has been explored (Aurora et al. 2004; Beydon et al. 2007b; Neve et al. 2006; Vilozi et al. 2005).

International guidelines (NHLBI 2002) recommend an initial evaluation and regular reeval-

uation for the assessment of the severity and the control of asthma. Asthma severity describes the underlying disease state as evaluated by FEV_1 and daytime and nighttime symptoms, all measured before treatment. Patients with moderate and severe persistent asthma are said to have values of 60–80 % and <60 % of predicted, respectively. FEV_1 may not be the best measure of severity in childhood asthma because most asthmatic children have FEV_1 values in the normal range independent of disease severity when clinically stable (Spahn et al. 2004). Diminished FEV_1 values in school-age children should identify children at risk of fixed airway obstruction at adulthood (Rasmussen et al. 2002). For children, FEV_1/FVC appears to be a more sensitive measure of severity in the impairment domain (NHLBI 2007).

A concave shape on the F/V curve may be observed as a result of small airway obstruction (Pellegrino et al. 2005). It may be observed in asthmatic children with a normal FEV_1 , together with a significant improvement following administration of a bronchodilator (Basek et al. 2005; Brand and Roorda 2003). A concave shape is associated with impairment in the FEF between 25 and 75 % of FVC ($FEF_{25-75\%}$) that is believed to measure peripheral airway obstruction. $FEF_{25-75\%}$ is among the first parameters to be abnormal in pediatric asthma and often the most significantly impaired of all spirometric measures (Paull et al. 2005; Spahn and Chipps 2006). A $FEF_{25-75\%} \leq 65\%$ is well correlated with bronchodilator responsiveness in asthmatic children with normal FEV_1 and may suggest suboptimal asthma control (Simon et al. 2010).

4.4.2.1.2 Lung V

Plethysmography may show lung distension/air trapping with larger RV and TLC in children than in adults (Jenkins et al. 2003). The RV is a sensitive parameter of airway obstruction in children, and a decrease in RV after bronchodilator administration appears to be specific for asthma diagnosis (Walemies 1998). Air trapping may be observed when FVC and FEV_1 values are normal in mild or moderate asthma (Cooper et al. 1977) or in controlled asthma (Vilozni et al. 2009).

Indeed, the principal event taking place in the asthmatic lung is the closure of small airways with increase in RV that is associated to a protective increase in TLC to preserve the functional range of FVC. Once the limit of the chest wall expansion has been reached, further increase in RV will result in falls in both FVC and FEV_1 (Irvin and Bates 2009).

FRC may be elevated, due to airway closure and/or dynamically elevated with an increased expiratory time constant (Stanescu 1999). It is a compensatory mechanism that minimizes the increase in R_{aw} and the expiratory flow limitation in obstructive airway disease. Hence, at an early stage of the disease, an isolated increase in lung V may be the sole functional abnormality (Landau et al. 1979; Paton 2000). In asthmatic children, FRC increases with severity of asthma (Greenough et al. 1987) and is more elevated in symptomatic children (Pool et al. 1988). Trapped air is associated with hypoxemia (Wolf et al. 1983) but correlates poorly with F limitation and may be lacking in patients with severe asthma (Basek et al. 2005; Desmond et al. 1986). In preschool children with asthma, a 6-week inhaled corticosteroid therapy is associated with reduced hyperinflation as indicated by lower FRC helium (Greenough et al. 1988). Bronchodilators were shown to decrease helium FRC in 80 % of children aged 2–7 years, and the decrease was correlated to baseline FRC. Some children exhibited an increase in FRC after bronchodilation when baseline value was low (Greenough et al. 1989).

4.4.2.1.3 R Measurement in Preschool Children

Higher baseline R_{int} measurement was shown in young preschool asthmatics (Beydon et al. 2003; Nielsen and Bisgaard 2001) and children with a history of wheeze (McKenzie et al. 2000) compared with healthy children. Children with persistent wheeze were shown to have higher R_{int} value than those with transient or no previous wheeze, but there was an overlap in R_{int} values between the three groups (Brussee et al. 2004). Using FOT, increased R of the respiratory system at 5 Hz has been reported in asymptomatic asthmatic preschool children as

compared with healthy subjects in some studies (Nielsen and Bisgaard 2001). Plethysmographic specific R_{aw} (sR_{aw}), product of R_{aw} and plethysmographic thoracic gas volume (TGV) may be altered by both hyperinflation and decreased airway diameter. In preschool children, it was shown to be increased in children with a history of wheeze (Lowe et al. 2002); it was able to identify responses to bronchodilators (Nielsen and Bisgaard 2001) and inhaled steroids (Nielsen and Bisgaard 2000). sR_{aw} was more strongly related to FEF after 50 % of FVC has been exhaled (FEF_{50%}) than to FEV₁ and could be used in preschool children to predict mild airflow limitation (Mahut et al. 2009). However, there is no established cutoff for sR_{aw} to separate healthy subjects from asthmatics (Marchal and Schweitzer 2005).

4.4.2.2 Cystic Fibrosis (CF)

In CF, the combination of mucus retention, bacterial infections, and inflammation results in obstructive lung disease primarily involving the small airways (Bedrossian et al. 1976; Fox et al. 1974; Ratjen and Grasemann 2005). Restrictive alterations develop secondary to the damage of lung parenchyma by inflammatory changes and by neutrophil degradation products. Chronic airway infection, progressing to bronchiectasis, gas trapping, and hypoxemia and hypercarbia, is the hallmark of CF lung disease. Pulmonary insufficiency is responsible for at least 80 % of CF-related death (Cystic Fibrosis Foundation 2008).

4.4.2.2.1 FEVs and FEFs

FEV₁ is the gold standard for lung function in CF. FEV₁ reflects the progression of pulmonary disease and correlates with mortality. An FEV₁ of less than 30 % predicted in conjunction with other clinical indicators is used for selecting suitable candidates for lung transplantation (Kerem et al. 1992).

In CF, obstruction primarily affects the small airways. An early change associated with airflow obstruction in small airways is a concave shape on the F/V curve and a reduction in the FEF_{25–75%} (Pellegrino et al. 2005) such as

reported in CF patients (Corey et al. 1997; 1976). This FEF often shows abnormalities in patients in whom FEV₁ is in the normal range. However, the large interindividual variability of this FEF must be taken into account in its interpretation.

Diminished FEVs and FEFs have also been reported in sedated infants with CF (including infants considered to be asymptomatic by their physician) using the raised volume rapid thoracoabdominal compression technique (Ranganathan et al. 2002; 2001) and in preschool children using incentive spirometry (Kozłowska et al. 2008; Marostica et al. 2002; Viložni et al. 2007).

4.4.2.2.2 Lung V Measurements and Other Techniques Detecting Small Airway Obstruction

AFO in small airways is associated with lung hyperinflation as indicated by increased RV, RV/TLC, and TLC.

A small airway obstruction syndrome with decreased VC and FEV₁, increased RV, but a normal FEV₁/VC ratio and TLC has also been described (Stanescu 1999). The condition is attributed to premature closing of airway leading to air trapping as demonstrated by high-resolution computed tomography (HRCT) scans (Cotes et al. 2006).

Studies using body plethysmography have provided evidence for trapped gases in the majority of patients with CF (Beier et al. 1966). The ratio of RV to TLC that indicates hyperinflation, a key feature of CF lung disease, has been found to correlate with disease severity in numerous studies (Beier et al. 1966; Landau et al. 1979; Landau and Phelan 1973a). Percentage of children with hyperinflation and trapped gas increases with age, and children with severe hyperinflation at 6–8 years showed the most severe disease progression over time (Kraemer et al. 2006).

In children <6 years, FRC is the only lung volume that can be measured routinely. Hyperinflation is one of the earliest features of CF (Gappa et al. 2001). Elevated TGV has been found in CF infants (Beardsmore et al. 1988), and hyperinflation has been detected by the helium dilution technique in preschool children (Beydon et al. 2002). Multiple-breath washout methods (MBW) may be particu-

		Pre	Pred	%Pred	Post	%Pred	Post/Pre
FVC	[L]	3.00	3.28	92	3.22	98	107
FEV 1	[L]	1.98	2.73	73	2.66	97	134

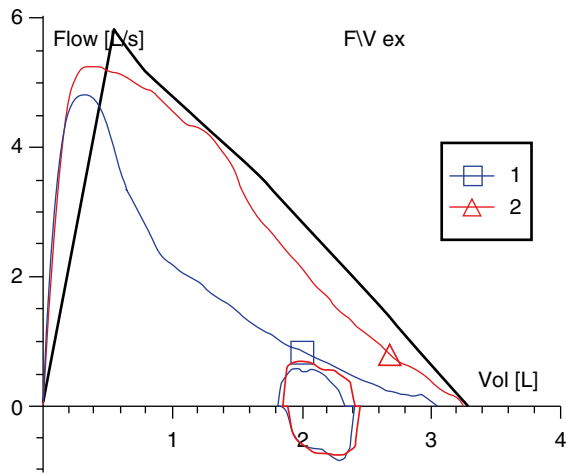


Fig. 4.14 A concave shape on the F/V curve may be observed in airflow obstruction. Airflow obstruction is often reversible in asthma with improvement in $FEV_1 \geq 12\%$ of baseline

larly sensitive to changes in peripheral lung function and detect early functional abnormalities in infant and preschool children with CF (Aurora et al. 2005; Ranganathan et al. 2008).

Frequency dependence of lung C as indicative AFO in small airways has been observed in the majority of CF, but the invasive nature of this technique limits its clinical use (Landau and Phelan 1973a). Alterations in lung elastic recoil were found with variable frequency (Cook et al. 1959; Landau and Phelan 1973a; Mansell et al. 1974).

4.4.2.2.3 Obstructive Ventilatory Defect

As the airway disease becomes more advanced and/or more central airways become involved, FEV_1 will be reduced out of proportion to the reduction in VC and an obstructive ventilatory defect be observed. Severity of lung disease in CF is classified by the degree of impairment in FEV_1 (with $FEV_1 < 50\%$ of predicted having severe disease) (Pellegrino et al. 2005), (Fig. 4.14). The obstructive ventilatory defect is reversible if an improvement in FVC and/or FEV_1 of at least 12 % of baseline after beta-adrenergic agents is observed (Pellegrino et al. 2005). Significant reversibility can be observed in 50–60 % of CF patients, and 10–20 % show

reduced lung function in response to short-acting inhaled bronchodilators (Brand 2000; Landau and Phelan 1973b; Shapiro et al. 1976).

Studies in CF have shown decreased C and increased R (Cook et al. 1959). Due to the large surface area of small airways, their contribution to R_{aw} is relatively small. R_{aw} measurements are therefore normal in many patients with CF until they develop disease involving the larger airways (Landau and Phelan 1973a). As the disease progresses, bronchial obstruction leads to tissue destruction with bronchiectasis and the development of areas of pulmonary emphysema and fibrosis. In more advanced disease, the destruction of lung tissue leads to decreased C that parallels the decline in FEV_1 (Hart et al. 2002). This increases respiratory load and favors a rapid and shallow breathing pattern that further impairs gas exchange in CF patients.

The loss of lung V that develops in patients due to tissue destruction as well as the hyperinflation decreases FVC: therefore FEV_1/FVC ratio may be normal even in patients with severe disease (Landau and Phelan 1973a).

4.4.2.2.4 Restrictive Ventilatory Defect

A small proportion of CF patients also develop a restrictive lung disease with decreased plethysmo-

graphic TLC. This restriction may be related to diffuse inflammatory obstruction of small airway and does not necessarily indicate more severe disease. It may be reversible in some (Ries et al. 1988).

4.4.2.3 Long-Term Sequelae of Neonatal Lung Disease and Chronic Lung Disease of Infancy (CLD)

Pulmonary disease resulting from a neonatal respiratory disorder is called chronic lung disease of infancy (CLD). Bronchopulmonary dysplasia (BPD) (defined as the need for supplemental oxygen for at least 28 days after birth) accounts for the vast majority of cases of CLD. What is now considered the “old” BPD was originally described in slightly preterm newborns who had been exposed to aggressive mechanical ventilation and high concentrations of inspired oxygen. Diffuse airway damage, smooth muscle hypertrophy, neutrophilic inflammation, and parenchymal fibrosis reflected extensive disruption of relatively immature lung structures. The “new” form of BPD is interpreted as a developmental disorder: despite being delivered several weeks before alveolarization begins, these infants often have only mild respiratory distress syndrome at birth, but lung development is affected with interruption of alveolarization at a very early stage with subsequent alveolar–capillary hypoplasia (Baraldi and Filippone 2007b). Most of the information on long-term lung function in survivors of BPD refers to patients who had the condition before surfactant treatment was available (“old” form of BPD).

4.4.2.3.1 In the First Months of Life

In the first months of life, survivors of BPD are severely affected. Infants with BPD at 28 days of age have increased total and expiratory R and severe F limitation especially at low lung V (Hazinski 1990). Neonates and young infants with CLD have increased levels of FRC by plethysmography and decreased FRC values by nitrogen washout, suggesting the presence of trapped air (Wauer et al. 1998). Specific dynamic C (C_{dyn}) may be reduced by more than 50 % (Allen et al. 2003; Gerhardt et al. 1987b) by small airway narrowing but also by interstitial fibrosis, edema, and atelectasis (Hazinski 1990). Lung mechanics

measurement that reflects the severity of neonatal disease (i.e., C_{rs} at 10–20 days) has been shown to correlate with subsequent reduction in lung function in 2-year-old BDP (Baraldi et al. 1997b; Bhandari and Panitch 2006).

4.4.2.3.2 During Infancy and Early Childhood

During infancy and early childhood, an improvement of airway physiology is observed, and C_L improves over time (Baraldi et al. 1997b; Bhandari and Panitch 2006; Gerhardt et al. 1987b). Maximum flow rates at FRC were reported to increase significantly within the first 2 years along with a reduction in R_{aw} (Farstad et al. 1995; Trachsel and Coates 2005). However analysis of FEF shows that substantial AFO persists in numerous survivors of BPD and in preterm infants without BPD during the first 3 years of life (Baraldi et al. 1997b; Tepper et al. 1986b). The degree of airflow limitation in the first years of life seems to predict later pulmonary function (at 8 years) suggesting tracking of lung function with time, negligible “catch-up” growth of the lung, and irreversible early airway-remodelling process (Baraldi and Filippone 2007b).

4.4.2.3.3 School-Age Children

Body plethysmography studies in school children and adolescents generally reveal normal TLC with hyperinflation as reflected by an increased RV and RV/TLC ratio. Consistently children diagnosed with BPD are more prone to hyperinflation than prematurely born children without BPD. FRC is normal or mildly increased. Differences between FRC determined by helium dilution technique and by plethysmography may indicate the presence of trapped air (Trachsel and Coates 2005).

At the age of 8 years, C_{dyn} was reported to be 57 % of the control group, in BPD, and 74 % in prematurely born children without CLD (Parat et al. 1995; Trachsel and Coates 2005).

School-age children with a history of BPD have lower FEV_1 than children born at term or those born prematurely without lung disease. They also have a lower FVC and FEV_1/FVC ratio than children born at term (Allen et al. 2003; Bhandari and Panitch 2006). Data from 18 studies in children, adolescents, and young adults

show that spirometric values are consistently lower in survivors of BPD, at any age between 6 and 20 years, than in controls born at term with FEV₁ ranging from normal to severely decreased values (Baraldi and Filippone 2007b). Patients who were born prematurely but did not have BPD usually fare better, but they too may have airflow limitation at school age and later (Baraldi and Filippone 2007b). Asthma-like symptoms are often associated to spirometric evidence of airflow limitation in children who had BPD as infants. But airflow limitation is only partially reversed by β_2 -agonists in children suggesting a stabilized remodelling process. HRCT studies have documented scattered parenchymal fibrosis and architectural distortion in many survivors of BPD, findings that are unusual in children with asthma (Baraldi and Filippone 2007b).

There is no evidence that children with BPD born since the introduction of surfactant-replacement therapy (i.e., “new” BPD) have better spirometric results at school age than those born in the pre-surfactant era (i.e., “old” BPD) as shown in studies evaluating cohort of infants weighing less than 1,000 g at birth or who were born before a gestational age of 29 weeks (Doyle 2006; Halvorsen et al. 2006). These results suggest that prematurity itself has a very important independent influence on the long-term respiratory prognosis (Baraldi and Filippone 2007b).

4.4.2.4 Obstructive Airway Disease Following Hematopoietic Stem Cell Transplantation: Bronchiolitis Obliterans (BO)

Hematopoietic stem cell transplantation (HSCT) is an established therapy for many chemosensitive or radiosensitive malignancies in children. BO is the most common late noninfectious pulmonary complication (i.e., that presents after the first 100 days following transplantation) with 80 % of cases occurring between 6 and 12 months. The reported incidence range is 0–48 % (Soubani and Uberti 2007). BO seems to be less common in children than in adults (Cerveri et al. 2005).

The most important association with BO is chronic graft versus host disease (GVHD), especially progressive chronic GVHD which evolves without hiatus from active acute GVHD. Most

cases of BO are thought to be secondary to bronchial mucosal damage from GVHD with inflammation of the small airways and subsequent obliteration. The main symptoms associated with BO are dry cough, dyspnea, and wheezing. Twenty percent of patients are asymptomatic.

Spirometry is the main tool to diagnose and follow up patients with BO following HSCT. Based on the experience of lung transplantation, a “BO syndrome” has been defined by PFT rather than histology (Estenne et al. 2002). It was suggested that the diagnosis of BO is made when there is evidence of (1) new onset of AFO with reduction in FEV₁ < 75 % of predicted with a FEV₁/FVC < 0.70 not responsive to bronchodilators; (2) air trapping or small airway thickening or bronchiectasis on HRCT of the chest with inspiratory and expiratory cuts with non-parenchymal involvement, RV on PFT > 120 % of predicted or pathological confirmation of constrictive bronchiolitis; and (3) absence of infection in the respiratory tract documented by clinical symptoms, radiological studies, or microbiological cultures (Soubani and Uberti 2007).

There are some studies that suggested that a reduction in mean FEF_{25–75} % may precede the decline in FEV₁ and is a sensitive but not specific indicator of subsequent development of BO (Estenne et al. 2000; Ouwens et al. 2002; Patterson et al. 1996; Reynaud-Gaubert et al. 2000). A pediatric study defined AFO as FEV₁ < 80 % and FEF_{25–75} < 60 % of predicted (Schultz et al. 1994).

Since the evolution of the disease despite treatment is particularly negative with a progressive worsening of respiratory function and a high mortality, early diagnosis is important. This can be achieved by systematic regular monitoring of the respiratory function starting from the onset of acute GVHD (Cerveri et al. 2005).

4.4.3 Neuromuscular Disease (NMD)

Decrease in VC is closely linked to weakness of respiratory muscles and disease progression. VC below 40 % predicts nocturnal alveolar hypoventilation, and VC < 25 % or < 1 L, in Duchenne

patients, is strongly associated with respiratory failure. In mild respiratory muscle weakness, VC is less sensitive than maximum respiratory pressures.

In patients with neuromuscular disorders, respiratory failure may present either acutely as a result of pneumonia or more slowly, as a result of progressive ventilatory decompensation. DMD and SMA account for the majority of patients seen in pediatric practice.

4.4.3.1 Lung V

The most frequently noted abnormality of lung V in patients with respiratory muscle weakness is a reduction in VC. VC can be measured in cooperative children, usually older than 6 years. VC reflects the strength of both inspiratory and expiratory muscles but is not specific, as it can be reduced by other factors than muscle weakness, such as reduction in both C_L (Gibson et al. 1977) and C_{CW} in patients with chronic respiratory muscle weakness (De Troyer et al. 1980). The decreased C_{CW} probably results from stiffening of tendons and ligaments of the rib cage and ankylosis of the costosternal and thoracovertebral joints (Laghi and Tobin 2003). A decrease in C_L could be related to diffuse microatelectasis in a few patients (Estenne et al. 1993).

In children younger than 4 years with NMD, higher C_{CW} normalized to body weight than in controls has been reported (Papastamelos et al. 1996). Such a high C_{CW} results in chest wall deformation during tidal breathing and excessive work of breathing. It also predisposes to atelectasis and can result in fixed deformation of the chest wall (i.e., pectus excavatum). Absence of lung stretch with sigh breaths and chest wall deformities can also result in reduced lung growth for children with NMD (Bach and Bianchi 2003; Panitch 2009).

In patients with NMD, a decrease in VC is an early sign of respiratory impairment. Decrease in VC and TLC is closely linked to a weakness of respiratory muscles (Braun et al. 1983; Hahn et al. 1997; Ragette et al. 2002) and disease progression (Inkley et al. 1974; Samaha et al. 1994). In patients with advanced NMD, a restrictive ventilatory defect is observed with TLC reduction.

In DMD, a typical evolution of lung V is observed (Hahn et al. 1997). In ambulatory DMD the lung V increases with age (ascending phase), and predicted V is almost normal (Tangsrud et al. 2001). With loss of ambulation between 7 and 12 years (Gozal 2000), measured VC remains stable (plateau phase), but % predicted values begin to decline. In the following years, VC declines by about 200 mL or 6–8 % per year (descending phase) (McDonald et al. 1995; Phillips et al. 2001; Rideau et al. 1981).

In SMA, there is a characteristic pattern of involvement with intercostal muscle weakness and relative sparing of the diaphragm (Kuzuhara and Chou 1981; Perez et al. 1996). The rib cage is neither stabilized nor expanded during inspiration. Over a period of time, the retraction of the rib cage has a detrimental effect on alveolar development. In type 1 SMA, with disease beginning before birth, pulmonary hypoplasia has been described (Cunningham and Stocks 1978). The best parameter to monitor respiratory muscle strength in children with SMA over 6 years is FVC (% predicted) (Manzur et al. 2003). In SMA, lung V (% predicted) decreases with age, with a greater VC decrease in type 2 than in type 3 SMA. A decline in VC from 87 to 73 % was shown to occur in type 3 SMA from 12 to 18 years (Souchon et al. 1996). The FVC may therefore be normal or near normal in stronger ambulant type 3 SMA (Samaha et al. 1994). In type 2 SMA, FVC is more severely impaired and was shown to decline from 55 % predicted to 37 %, from 10 to 16 years, with a yearly average decline by 2–5 % between 7 and 15 years of age (Barois et al. 2005; Herridge et al. 2003; Souchon et al. 1996). A restrictive pattern was observed in a majority (70 %) of type 2 SMA children followed longitudinally (Carter et al. 1995). In intermediate type 1 SMA, severe impairment in FVC has also been described (Barois et al. 2005) with progressive decrease in FVC from 60 % predicted (at 7 years) to 16 % (at 15 years) in children without tracheotomy and from 22 % predicted (at 7 years) to 14 % (at 15 years) in children with tracheotomy (Ioos et al. 2004).

Progression of scoliosis seems to contribute to VC decline in children with NMD (Miller et al.

1988), but treatment of scoliosis with spinal stabilization did not prevent further VC decline in patients with DMD (Kennedy et al. 1995; Miller et al. 1988). In type 2 SMA, beneficial effects of spinal surgery on pulmonary function remain controversial (Mullender et al. 2008; Wang et al. 2007), but the rate of pulmonary function decline may be slowed (Wang et al. 2007).

Static lung V may also be affected in some NMD patients by coexistent lung or airway disease (American Thoracic Society, European Respiratory Society 2002).

Measurement of postural change in VC gives a simple index of weakness of the diaphragm relative to the other inspiratory muscles. A fall of 30 % or more in the supine compared with the erect posture is generally associated with severe diaphragmatic weakness (American Thoracic Society, European Respiratory Society 2002). Studies in adults with generalized NMD suggest that supine VC is a simple, sensitive, and specific test for diaphragm weakness and can replace invasive diagnostic tests (Fromageot et al. 2001; Lechtzin et al. 2002).

Thresholds of VC have been identified to predict treatable complications and outcome in patients with NMD. A VC below 60 % is a sensitive and specific predictor of the onset of sleep-disordered breathing; VC below 40 % predicts nocturnal alveolar hypoventilation, and $VC < 25\%$ or $< 1\text{ L}$, in DMD, is strongly associated with respiratory failure and poor survival unless patients are treated with mechanical ventilation (Baydur et al. 1990; Canny et al. 1989; Hukins and Hillman 2000; Mellies et al. 2003; Phillips et al. 2001, 1999; Ragette et al. 2002; Simonds et al. 1998; Wallgren-Pettersson et al. 2004).

RV is usually normal or increased, the latter, particularly with marked expiratory weakness (Kreitzer et al. 1978). Consequently, TLC is less markedly reduced than VC, and the RV/TLC and FRC/TLC ratios are often increased without necessarily implying airway obstruction (American Thoracic Society, European Respiratory Society 2002). A hypodynamic type of ventilatory defect with increased RV, low VC, and normal TLC can

be observed early in the course of NMD. Such a presentation has recently been described in patients with DMD (Tangsrud et al. 2001). These children may later exhibit chest wall deformities leading to a true restrictive syndrome.

4.4.3.2 F/V Curves

R_{aw} is normal in uncomplicated respiratory muscle weakness. The maximum expiratory and maximum inspiratory F/V curves characteristically show a reduction in those F that are most effort dependent, that is, maximum expiratory F at large lung V (including PEF) and maximum inspiratory F at all lung V . With severe expiratory weakness, an abrupt fall in maximum expiratory F is seen immediately before RV is reached (Vincken et al. 1987). Oscillations of maximum expiratory and/or inspiratory F , the so-called sawtooth appearance, are seen particularly when the upper airway muscles are weak and in patients with extrapyramidal disorders (American Thoracic Society, European Respiratory Society 2002; Vincken and Cosio 1989).

4.4.3.3 Respiratory P

In mild respiratory muscle weakness, VC is less sensitive than maximum respiratory P measurement. VC is normal, or only minimally reduced, if respiratory muscle strength is more than 50 % of predicted (Laghi and Tobin 2003). This finding results from the sigmoid shape of the P/V relationship of the respiratory system.

Several invasive and noninvasive tests to assess respiratory muscle strength have been reported to be of value in testing respiratory muscle strength in patients with NMD. In children, normative data are only available for P_{Imax}, P_{E_{max}}, and sniff nasal inspiratory pressure (SNIP).

P_{Imax} and P_{E_{max}} are tests of global inspiratory and expiratory muscle strength. They were found to be reduced in NMD patients (Baydur 1991; Black and Hyatt 1971). The P_{Imax} decline was related to the decline of inspiratory reserve volume and TLC, and the P_{E_{max}} decline was related to the decline of ERV and the increase of RV in children and adults with DMD (Hahn et al. 1997).

In DMD, earlier in the course of the disease, inspiratory muscle strength evaluated by P_Imax remained relatively well preserved (as compared with P_Emax) implying relative sparing of the diaphragm (Hahn et al. 1997; McDonald et al. 1995). In patients with diaphragm weakness, a VC decline of 25 % or more following supine positioning is associated with a mean P_Imax decline of 18 ± 14 % (Ragette et al. 2002). Sleep-disordered breathing usually develops when P_Imax is less than 45 cm H₂O. Diurnal hypercapnia is likely when respiratory muscle strength falls to 35 cm H₂O (Ragette et al. 2002).

The sniff is a natural maneuver which many children find much easier to perform than P_Imax. Inspiratory muscle strength can easily be assessed by SNIP in children with NMD (Stefanutti et al. 2000). A recent report comparing SNIP and P_Imax in 241 patients with NMD found that the values of P_Imax were at least the same or even greater than the SNIP, particularly in patients with severe ventilatory restriction. This can be explained by the fact that patients with severe neuromuscular disorders may not be able to perform a rapid sniff maneuver owing to significant muscle atrophy (Hart et al. 2003).

The reduction of P_Emax is the first sign of respiratory muscle dysfunction in DMD children (Hahn et al. 1997; McDonald et al. 1995). Expiratory muscles that contribute to P_Emax are primarily the abdominal muscles, and their strength normally exceeds that of inspiratory muscles (American Thoracic Society, European Respiratory Society 2002). Therefore P_Emax < P_Imax indicates prevailing expiratory muscle weakness, a characteristic for children with type 2 and 3 SMA (Carter et al. 1995). Recurrent chest infections may therefore occur early in SMA children due to a predominance of expiratory muscle weakness with insufficient cough and retention of airway secretions. In patients with muscular dystrophies, P_Emax >45 cm H₂O has been found to be necessary for an effective cough

(Mellies and Dohna-Schwake 2005; Mellies et al. 2001; Szeinberg et al. 1988).

Assessment tools to measure the different components of cough include also inspiratory VC (IVC) and the peak expiratory flow or peak cough flow (PCF). Expiratory muscle weakness is often associated with a decrease in PCF and ERV. The effect of coughing can be visualized on the maximum expiratory *F/V* curve in healthy subjects as a transient *F* exceeding the maximum achieved during forced expiration. The absence of such supramaximal *F* transients during coughing presumably results in impaired clearance of airway secretions and is associated with more severe expiratory muscle weakness (American Thoracic Society, European Respiratory Society 2002; Polkey et al. 1998). Patients who could not generate peak *F* transients had significantly reduced PEF, FVC, and P_Emax values ≤ 45 cm H₂O (Szeinberg et al. 1988).

Impaired coughing leads to mucus retention, atelectasis, and recurrent pneumonia. In adults with NMD, PCF below 160–200 L/min is associated with insufficient clearance of airway secretions (Bach and Saporito 1996). PCF (below 160 L/) and IVC <1.1 L seem also to be able to identify children with NMD at high risk for severe chest infections (Dohna-Schwake et al. 2006). Baseline PCF measurements above 160 L/min, however, do not guarantee adequate airway clearance, because respiratory muscle function can deteriorate during respiratory infections (Labanowski et al. 1996). For this reason a peak cough expiratory flow rate of 270 L/min has been used to identify patients who would benefit from assisted cough techniques (Finder et al. 2004; Laroche et al. 1988). In DMD, the likelihood of having a PCF value <270 L/min has been shown to rise significantly when FVC is <2.1 L (Gauld and Boynton 2005).

The illustrations presented in this paper were captured with the Jaeger program 5.20.0.52 (Viasys Healthcare, Höchberg, Germany).

Essentials to Remember

- A restrictive ventilatory defect of pulmonary origin is usually associated with a decrease in lung C (C_L) that can be due to an increase in the quantity of interstitial tissue in the lung, like in interstitial lung disease (ILD), pulmonary fibrosis, infiltration, or edema. Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) result from pulmonary edema and inflammation.
- Restrictive defect that arises in the chest wall as a consequence of severe obesity or disease process affecting the ribs or the vertebral column, such as kyphoscoliosis, is associated with reduction in C_{CW} .
- In restrictive diseases, expansion of the lung is restricted because of alterations in lung parenchyma or as a consequence of extraparenchymal diseases affecting pleura, chest wall, or neuromuscular apparatus. A restrictive ventilatory defect is

observed in these diseases with reduction in total lung capacity (TLC) and normal forced expiratory volume in 1 s (FEV_1)/vital capacity (VC) ratio.

- Obstructive diseases of the lung are extremely common. Airflow limitation is a functional consequence of asthma and chronic obstructive pulmonary disease (chronic bronchitis, emphysema), cystic fibrosis (CF), bronchiectasis, and bronchiolitis. Airflow limitation is also observed in bronchiolitis obliterans (BO). An obstructive defect is defined by a reduced FEV_1 /VC ratio. Severity of lung function impairment is based on FEV_1 % of predicted ($FEV_1 < 50$ % corresponding to severe impairment). Airflow obstruction (AFO) is often reversible in asthma with improvement in FEV_1 and/or FVC ≥ 12 % of baseline (Fig. 4.15). AFO in small airways is suspected from a concave shape on the

		Pre	Pred	%Pred	Post	%Pred	Post/Pre
FVC	[L]	2.75	3.64	76	2.79	77	101
FEV 1	[L]	1.39	3.17	44	1.48	47	107
FEV 1 % VC MAX	[%]	47.22	84.35	56	48.80	58	103

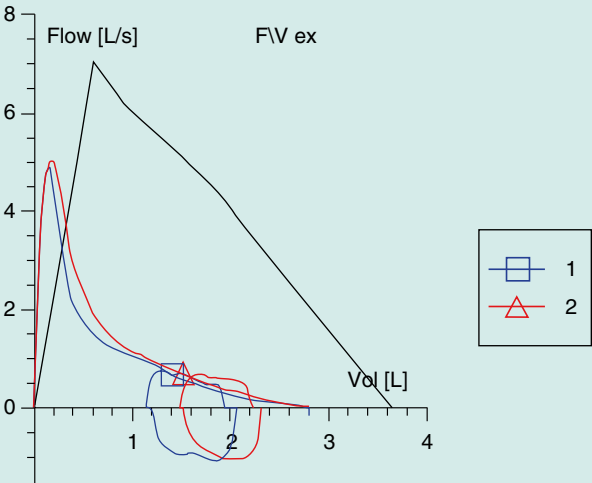


Fig. 4.15 In cystic fibrosis, as the airway disease becomes more advanced and/or more central airways become involved, FEV_1 will be reduced out of proportion to the reduction in vital capacity (VC) and an

obstructive ventilatory defect be observed with a reduced FEV_1 /VC ratio. A $FEV_1 < 50$ % predicted corresponds to severe impairment of lung function

expiratory *F/V* curve. AFO in small airways is associated with lung hyperinflation. In children with asthma an isolated increase in lung volume may be the sole functional abnormality. Hyperinflation is one of the earliest features of CF.

- Decrease in VC is closely linked to weakness of respiratory muscles and disease progression. VC reflects the strength of both inspiratory and expiratory muscles, but it can be reduced by other factors than muscle

weakness (as decreased C_L and C_{CW}). A fall of 30 % or more in the supine compared with the erect posture is associated with severe diaphragmatic weakness. VC below 40 % predicts nocturnal alveolar hypoventilation, and VC <25 % or <1 L, in Duchenne patients, is strongly associated with respiratory failure. In mild respiratory muscle weakness, VC is less sensitive than maximum respiratory pressures (P_{Imax}, P_{E_{max}}, sniff nasal inspiratory pressure (SNIP)).

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Part II

Basics of Respiratory Support and Mechanical Ventilation

Neonatal Intubation (Specific Considerations)

5

Xavier Durrmeyer and Claude Danan

Educational Aims

- To understand the physiological consequences of awake laryngoscopy and endotracheal intubation
- To underline the specificities related to neonatal intubation and its possible complications and side effects
- To provide general recommendations for clinical management of neonatal intubation

5.1 Introduction

Although first described in animals in mythologies and ancient civilizations (Raju 1999), neonatal endotracheal intubation was first recommended as resuscitation practice at birth in Parisian maternities at the beginning of the nineteenth century (Obladen 2009). Techniques and opinions relative to this practice dramatically evolved in the next years until it was finally considered as a life-saving practice for compromised newborns in the late 1920s and early 1930s. This procedure requires specific skills due to potentially

life-threatening situation, small size of babies, and particular physiological status of newborns. This chapter will cover the specificities of neonatal intubation regarding its physiological effects, possible adverse effects, and recommended practice.

5.2 Physiological Effects

This paragraph will expose the physiological changes induced by awake intubation. Indeed when premedication is used, it is virtually impossible to differentiate the effects of the procedure from the effects of the drugs. However, as will be discussed in the third paragraph, premedication should be used whenever possible prior to neonatal intubation.

5.2.1 Hemodynamic Changes

5.2.1.1 Heart Rate

The effects of endotracheal intubation on heart rate are difficult to identify since most studies used premedication with atropine or glycopyrrolate even for infants experiencing awake intubation (Friesen et al. 1987; Stow et al. 1988; Millar and Bissonnette 1994). However, one study compared three groups receiving either no medication (control), atropine alone, or atropine + suxamethonium (Kelly and Finer 1984). Heart rate was significantly decreased by the intubation procedure in the first two groups, although no severe

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bradycardia <80 bpm was observed in the atropine group in contrast to the control group. In one study including a group of 15 term newborns experiencing awake intubation (one patient had received atropine), there was a non-significant increase in heart rate, although methods and frequency of measurements are not detailed (Charlton and Greenhough 1988). In other studies where vagolytic premedication was systematic, little change in heart rate occurred in any group regardless the use of anesthesia (Stow et al. 1988; Millar and Bissonnette 1994). One should notice that infants in these studies were term newborns who are less prone to bradycardia than preterm newborns.

5.2.1.2 Arterial Blood Pressure

The effects of laryngoscopy and intubation on blood pressure are debated. Although a majority of study report a transient but significant increase in blood pressure during awake laryngoscopy (Friesen et al. 1987; Millar and Bissonnette 1994; Kelly and Finer 1984), one study specifically examined the effects of intubation on blood pressure and found no effect of laryngoscopy on this parameter in a small group of term newborns (Charlton and Greenhough 1988). Another issue to be explored is the potential long-term consequences of blood pressure variations. No clinical study addressed this important question, but sudden changes in blood pressure are classically considered as a risk factor for intracranial hemorrhage (McDonald et al. 1984).

5.2.2 Respiratory Changes

Detailed pulmonary mechanics during neonatal endotracheal intubation have never been studied due to the technical difficulties of evaluating respiratory parameters in newborns. However, physiological characteristics of newborns include lower oxygen reserve and greater consumption, when compared to adults or older children (see Part I of this book). In ten preterm infants, Marshall et al. reported that laryngoscopy could cause apnea, airflow obstruction, and decreased

transcutaneous oxygen tension (Marshall et al. 1984). In addition, it has been shown that the time until onset of desaturation in apneic children increases with age (Patel et al. 1994). Therefore newborns are at high risk for desaturation very soon after removal of oxygen supply or withholding of efficient ventilation. This situation has many practical consequences for the realization of the procedure (see paragraph 3). One might also suppose that the use of premedication could also influence the occurrence of desaturations, especially if spontaneous breathing is removed by the use of respiratory depressive drugs or muscle blocker. However, randomized controlled trials comparing morphine (Lemyre et al. 2004), thiopental (Bhutata et al. 2000), or succinylcholine (Barrington et al. 1989) to placebo found no difference between groups in the incidence of desaturations. In studies evaluating different premedication protocols for preterm infants, desaturations – although differently defined between studies – usually happen in at least 50 % of cases (Roberts et al. 2006; Ghanta et al. 2007).

5.2.3 Neurological Effects

5.2.3.1 Intracranial Pressure

All studies on this topic have shown a significant increase in intracranial pressure (ICP) during awake intubation (Friesen et al. 1987; Stow et al. 1988; Millar and Bissonnette 1994; Kelly and Finer 1984; Raju et al. 1980). Increased ICP has been considered a risk factor for intracranial hemorrhage (McDonald et al. 1984; Donn and Philip 1978), although more complex mechanisms are involved (Whitelaw 2001). Several potential physiological mechanisms of increased ICP during intubation have been proposed such as infant's struggling, hypoxemia, increased PaCO₂, increased cerebral blood flow, or impeded cerebral venous return via increased intrathoracic pressure and/or hyperextension of the neck. However Doppler measurements have shown that cerebral blood flow velocities were not related to intracranial pressure changes (Millar and Bissonnette 1994), and apnea lasting 30 s

was not correlated to increased ICP (Fisher et al. 1982). Therefore, the factors contributing to ICP increase during awake intubation are probably the infant's struggling and the decrease in cerebral venous return. This hypothesis is confirmed by the fact that paralysis prior to intubation only partly attenuates the increase in ICP (Stow et al. 1988; Kelly and Finer 1984).

5.2.3.2 Pain

Evaluation of pain in the newborn is extremely challenging. Moreover, most pain scales include facial expressions which cannot be properly evaluated for technical reasons during laryngoscopy. Many physiological changes such as bradycardia, increased blood pressure, or desaturation can be expressions of pain in the newborn, but these phenomena are extremely frequent during endotracheal intubation and can be attributable to the physiological characteristics of the newborn (see upper paragraphs). Nevertheless, laryngoscopy and endotracheal intubations are known to be painful in children and adults. Newborns are known to have physiological and anatomical equipment to feel pain from 20 weeks of gestational age (Derbyshire and Furedi 1996). Preterm newborns have a lower threshold for painful stimuli (Fitzgerald et al. 1988). Then it would seem unethical to perform a nonemergent or elective endotracheal intubation in a term or preterm newborn without providing efficient analgesia.

5.3 Specific Difficulties and Complications of Neonatal Intubation

5.3.1 Neonatal Upper Airways

In addition to the small size of patients and anatomical entities, newborns show upper airway specificities. They usually have anterior larynx, a relatively large tongue, and a U-shaped epiglottis. This combination makes visualization of the glottis rather difficult, when compared to older infants or adults.

5.3.2 Indications for Intubation

Considering growing use of noninvasive ventilation in neonatal respiratory distress, the indications for endotracheal intubation are still debated to date (Finer 2008). Even recent recommendations on neonatal resuscitation state that endotracheal intubation can be considered at different steps but is not mandatory (The International Liaison Committee on Resuscitation 2006). It is then impossible to establish a consensus on firm indications for endotracheal intubations. However, most neonatologists agree on the following indications:

- Emergency intubation: failure of bag mask or laryngeal mask ventilation, prolonged resuscitation, prophylactic surfactant administration, diaphragmatic hernia, and upper airway abnormality
- Semi-elective or elective intubation: respiratory acidosis ($\text{pH} < 7.20$ and $\text{PCO}_2 > 65$ mm Hg), apnea and/or bradycardia in spite of noninvasive ventilation, curative surfactant administration, hypoxia (definitions may vary), tube change, and planned surgery requiring general anesthesia

5.3.3 Complications of Neonatal Intubation

This topic will be more extensively addressed in the following chapter. We should mention some of the most frequent or specific complications observed after neonatal intubation, such as subglottic stenosis (which is possibly highly dependent on tube size (Contencin and Narcy 1993)), trauma (Krause and Hoehn 1998), or even light bulb ingestion (Naumovski et al. 1991). As mentioned earlier in this chapter, the most frequent adverse event observed during intubation is desaturation, occurring in around 50 % of cases in preterm infants, regardless the type of premedication used. Bradycardia is often observed during neonatal intubation with different possible causes such as vagal stimulation, hypoxia, or pain. The incidence of these adverse events observed in the most recently published studies are summarized in table 5.1.

Table 5.1 Frequency of desaturation and bradycardia in the studies published after 2000

Study	Premedication	Population (median values or range for gestational age and birth weights)	Desaturation	Bradycardia
Oei (2002)	Placebo	<i>N</i> =10 30 weeks – 1,160 g	Missing data	Maximal heart rate drop – 62±46 bpm
	Morphine + atropine + suxamethonium	<i>N</i> =10 29 weeks – 1,077 g	Missing data	Maximal heart rate drop – 28±41 bpm
Lemyre (2004)	Placebo	<i>N</i> =17 27 weeks – 904 g	82 % SpO ₂ <85 %	71 %
	Morphine	<i>N</i> =17 28 weeks – 1,065 g	100 % SpO ₂ <85 %	94 %
Milesi (2006)	Nitrous oxide	<i>N</i> =26 30 weeks – 1,540 g	69 % SpO ₂ <85 %	0 %
Dempsey (2006)	Atropine + fentanyl + mivacurium	<i>N</i> =33 29 weeks – 1,360 g	88 % SpO ₂ <80 %	9 %
Roberts (2006)	Atropine + fentanyl	<i>N</i> =20 30 weeks – 1,627 g	80 % SpO ₂ <85 %	5 %
	Atropine + fentanyl + mivacurium	<i>N</i> =20 30 weeks – 1,420 g	62 % SpO ₂ <85 %	14 %
Ghanta (2007)	Atropine + morphine + suxamethonium	<i>N</i> =30 28 weeks – 1,095 g	40 % SpO ₂ <80 %	37 %
	Propofol	<i>N</i> =33 27 weeks – 1,020 kg	50 % SpO ₂ <80 %	12 %
Pereira e Silva (2007)	Morphine + midazolam	<i>N</i> =10 28–34 weeks – >1,000 g	0 % (<i>data not shown</i>)	0 % (<i>data not shown</i>)
	Remifentanyl + midazolam	<i>N</i> =10 28–34 weeks – >1,000 g	0 % (<i>data not shown</i>)	0 % (<i>data not shown</i>)
Welzing (2009)	Remifentanyl	<i>N</i> =21 31 weeks – 1,560 g	0 % SpO ₂ <80 %	0 %

5.4 Recommendations for Clinical Practice

5.4.1 Technical Preparation

Equipment should be tested prior to intubation. Magill forceps, appropriate-sized blade, and tube should be available. Efficient suction and a hand ventilation device – if possible with positive end expiratory pressure – supplied with oxygen should be readily available. Preoxygenation is usually recommended, although no trial ever evaluated it in newborns. However, the weight of experience from anesthesiology and the rapid occurrence of hypoxia in apneic infants (Patel et al. 1994) strongly support this practice. In the preterm infant, oxygen can have deleterious

effects, especially causing retinopathy, and we do not recommend prolonged preoxygenation in this population. Experience is determinant in the success of the procedure for intubation in the delivery room (O'Donnell et al. 2006), but the use of a muscle relaxant in addition to a fast-acting opioid for nonemergent intubation has been reported as a facilitating factor for non-experienced personnel (Dempsey et al. 2006).

5.4.2 Intubation Route

Both oral and nasal route can be used for intubation. A meta-analysis including only two randomized controlled trials concluded that neither route was superior to the other and

that complications were comparable for both techniques (Spence and Barr 2000). Common sense certainly supports the use of the route the operator is most familiar with. However, a recent study evaluating intubation time in newborn mannequin for training found a significant reduction in intubation time when the oral route was used (Lenclen et al. 2009).

5.4.3 Premedication Use

A recent review on the use of premedication prior to intubation concluded that “Tracheal intubation without the use of analgesia or sedation should be performed only for urgent resuscitations in the delivery room or other life-threatening situations when intravenous access is unavailable” (Carbajal et al. 2007). In addition, recent recommendations from the American Academy of Pediatrics support the use of a premedication for nonemergent intubations (Kumar et al. 2010). Still, the most appropriate drug or drugs are still unknown. Association of an opioid and a muscle blocker is usually considered a traditional relatively safe and efficient combination (Carbajal et al. 2007; Kumar et al. 2010; Duncan et al. 2001). More recent works have shown that a single drug such as propofol (Ghanta et al. 2007) or remifentanyl (Welzing et al. 2009) might be as well efficient and safe. Concerning propofol systemic hypotension has been reported in premature infants (Papoff et al. 2008; Welzing et al. 2010). However, these new protocols require careful clinical evaluation through large randomized controlled trials assessing long-term outcomes.

5.4.4 Tube Positioning

5.4.4.1 Intratracheal Position

Direct visualization of the tube between the vocal cords and proper chest movement are obvious determinants of successful endotracheal intubation. However, unsuccessful intubation is frequent, especially in the delivery room reaching a rate of 38 % in a recent study (O'Donnell et al. 2006). Among nonclinical

Table 5.2 Recommended tube size and position according to patient's weight and intubation route

Baby's weight (g)	Tube size (internal diameter)	Tube length (cm) oral route	Tube length (cm) nasal route
500–750	2.5	5.5–6.0	6.5–7.0
750–1,000		6.0–6.5	7.0–7.5
1,000		7.0	8.0
1,500		7.5	8.5
2,000	2.5 or 3	8.0	9.0
2,500		8.5	9.5
3,000	3	9.0	10.0
3,500	3.5	9.5	10.5
4,000			11.0

devices exhaled carbon dioxide as determined by a carbon dioxide detector or capnography has proven to be a reliable tool (O'Donnell et al. 2006; Roberts et al. 1995).

5.4.4.2 Tube Length

The easiest rule to follow is the rule of 7-8-9 (7 cm at the lips for 1 kg, 8 cm for 2 kg, and 9 cm for 3 kg babies) (Peterson et al. 2006). Derived from this rule is the «7 + weight (kg)» rule for nasal intubation. In this case, the between the end of the tube and the patient's nare should be the sum of 7 plus the infant's weight. For example, proper tube positioning should occur at 8.5 cm for a 1.5 kg nasally intubated baby. However, these rules are not applicable to infants under 750 g. Other techniques such as foot length for nasal intubation (Embleton et al. 2001) can show a good accuracy but might be less feasible. See Table 5.2 for recommended tube placement. In some series, more than 50 % of tubes are misplaced (Thayyil et al. 2008; Kempley et al. 2008); therefore tube position should always be controlled by chest X-ray and be placed at the level of the first or second thoracic vertebrae (Thayyil et al. 2008).

Conclusion

Endotracheal intubation can be a life-saving procedure in compromised newborn. It is also a potentially harmful and certainly painful procedure with acute and possibly long-term consequences on the very reactive

physiological status of newborns (especially preterm infants). Experience and proper training are key determinants of successful and well-tolerated intubation. An efficient premedication should be used whenever possible. Further research works should determine the most appropriate indications for intubation and rigorously evaluate premedication policies.

Essentials to Remember

- Endotracheal intubation in neonates can be a life-saving procedure but is associated with acute changes in physiological parameters.
- Desaturations during the procedure are very frequent, but their long-term consequences are unknown.
- Awake intubation constantly increases intracranial pressure and is painful.
- Whenever possible, a premedication should be used prior to endotracheal intubation.
- Tube positioning should be carefully and frequently assessed since tube malposition is common in newborns.

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Oxygen Supplementation, Delivery, and Physiologic Effects

6

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Educational Aims

- Review the various oxygen delivery systems available to the pediatric and neonatal patient population.
- Describe the numerous central and peripheral ventilatory control centers.
- Discuss various therapies to treat pulmonary vasoconstriction and their mechanisms of action.
- Describe the appropriate physiologic response to oxygen supply.
- Describe the hemodynamic effects of oxygen supply and delivery.

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6.1 Introduction

The delivery of oxygen is a vital component of patient care within pediatric and neonatal intensive care units. Clinicians are constantly altering the support provided to each patient in an attempt to optimize global oxygen delivery as defined by the following equation:

$$\text{DO}_2 = \text{CO} \times \text{arterial O}_2 \text{ content}$$

$$\text{arterial O}_2 \text{ content} = \left(\text{SaO}_2 \text{ saturation} \times 1.39 \left(\text{mL/g} \right) \times \text{Hb} \right) + (0.003 \times \text{PaO}_2)$$

where DO_2 represents oxygen delivery; CO, cardiac output; SaO_2 , arterial oxygen saturation; Hb, hemoglobin; and PaO_2 , partial pressure of oxygen in arterial blood. Thus, decreased oxygen delivery can result from inadequate cardiac output, low arterial oxygen saturation, inadequate hemoglobin concentration, or low PaO_2 as a minor contributor (secondary to the factor of 0.003 in the formula outlined above). In this chapter, we will review the variety of mechanisms by which clinicians can improve the supply of oxygen to the patient to meet the metabolic demands involved with various pathophysiologic processes.

6.2 Oxygen Delivery Systems

The various methods to physically deliver oxygen depend on the patient's respiratory status and oxygen demands. In the neonatal and pediatric populations, the options are patient specific as body habitus, size, and tolerance for various oxygen delivery devices vary significantly. The most important factor is the gas flow rate since this determines if the oxygen delivery system is sufficient to meet a patient's inspiratory demand. If gas flow is inadequate, then in turn, the FiO_2 is likely to be variable and insufficient as the patient entrains room air. We can better delineate this concept by dividing the available delivery systems into low-flow and high-flow devices.

Low-flow devices tend to provide a less consistent concentration of inspired oxygen and include traditional nasal cannulae, simple face masks, and tracheostomy collars.

High-flow devices provide a more reliable concentration of inspired oxygen to the patient regardless of respiratory effort. These devices include partial and non-rebreather face masks, nebulizers, high-flow nasal cannulae, oxygen hoods, noninvasive ventilation (NIV), and mechanical ventilation.

6.2.1 Low-Flow Devices

6.2.1.1 Nasal Cannulae

Various sizes of nasal prongs are available for the neonatal and pediatric populations. Oxygen can be supplied from a wall or tank source at a rate of 1–6 liters/minute (L/min) for the pediatric population. This provides an approximate FiO_2 of 0.24–0.50. The actual FiO_2 delivered to the patient depends on the patient effort and the potential for entrainment of room air. Humidification is important to minimize drying of nasal and upper airway secretions. In addition, a blender with ambient air can be used to decrease flows to as low as 0.025 L/min, which can be especially useful in the premature neonatal population.

6.2.1.2 Simple Face Mask

Such a device fits over the nose and mouth and provides a gas flow rate of 6–10 L/min and FiO_2 of 0.35–0.60.

6.2.1.3 Venturi Face Mask or Tracheostomy Collar

This is a face mask with a controlled jet of high-flow oxygen which entrains a continuous flow of ambient air. Such a device allows a controlled provision of FiO_2 at 0.24, 0.28, 0.31, 0.35, 0.40, or 0.50. This approach can be crucial for patients with chronic carbon dioxide retention. The manufacturer lists the predetermined flow rates required to provide the chosen FiO_2 . The FiO_2 is dependable as long as the flow rate does not exceed the inspiratory demand of the patient.

6.2.2 High-Flow Devices

6.2.2.1 High-Flow Nasal Cannulae

In the neonatal intensive care unit (NICU), high-flow nasal cannula (HFNC) (>1 L/min for the neonatal population) has been introduced as an alternative to nasal continuous positive airway pressure (NCPAP) which has been the traditional standard of care for infants with respiratory distress syndrome (RDS) or apnea. Current HFNC devices deliver gases heated to near body temperature. These gases are saturated with water vapor and deliver typical gas flow of 1–5 L/min in the NICU population via a nasal cannula setup (Kubicki et al. 2008). This 1–5 L/min has a higher partial pressure than flow from a simple nasal cannula secondary to the degree of humidification. A theoretical concern with the use of HFNC has been the potential to produce an unknown and excessive pressure accumulation in the lungs. For a more in-depth review of this topic, please refer to Chap. 4 of this text.

6.2.2.2 Non-rebreather Face Masks

This delivery device combines a simple face mask with a reservoir bag and an inflow system for fresh gas, thus, allowing the system to theoretically deliver up to 100 % oxygen to the patient.

This is made possible by two separate one-way valves. One valve is located between the mask and the reservoir, while the other is located at the exhalation port. This setup ensures fresh gas delivery with each inspiration while preventing the exhaled gas from being rebreathed. A safety backup in the design allows a port to open in case the flow of oxygen is disrupted, such that the patient can then entrain room air with inspiratory effort.

6.2.2.3 Partial Rebreather Face Masks

This mask is essentially the same setup as the non-rebreather mask except there is no one-way valve between the mask and the reservoir. Therefore, exhaled gas can mix with the oxygen in the reservoir bag, and thus, the delivered fraction of inspired oxygen is less than 1.0.

6.2.2.4 Oxyhood

This device allows for the delivery of high-flow oxygen to a contained space surrounding the patient's head while allowing easy access for patient care. The FiO_2 quickly re-equilibrates after any movement of the hood, which could allow for potential entrainment of room air. The oxygen level must be continuously monitored near the patient's face as there is an increasing gradient in the FiO_2 from the top of the hood to the bottom due to the slight increase in density of oxygen (1.42 kg/m^3) as compared to room air (1.29 kg/m^3).

6.2.2.5 Noninvasive Ventilation (NIV)

This mode of ventilation and oxygen delivery can be effective in decreasing atelectasis, improving alveolar ventilation, and decreasing respiratory muscle fatigue in specific groups of neonatal and pediatric patients (RDS, neuromuscular disease). Unfortunately, there are minimal pediatric studies in the acute care setting and even less so in direct comparison with intubation and mechanical ventilation. NIV does allow for close control of FiO_2 from 0.21 to essentially 1.0. NIV is generally the preferred mode of support for patients with neuromuscular weakness and upper airway obstruction from poor pharyngeal tone and/or

enlarged tonsils and adenoids. Although there are a variety of nasal and full-face masks for large pediatric patients and adults, the options for infants and small children in the USA are limited. For a more in-depth review of this topic, please refer to Chap. 4 of this text.

6.2.2.6 Oxygen Delivery via Invasive Mechanical Ventilation

Invasive mechanical ventilation allows for complete control of the gas mixture being administered to the patient via an endotracheal tube. A FiO_2 of 1.0 can be delivered consistently regardless of patient effort, but this should be minimized to prevent oxygen toxicity to the lungs.

6.2.2.7 Hyperbaric Oxygen

Hyperbaric oxygen therapy is appropriate for those clinical conditions involving severely impaired oxygen delivery and altered hemoglobin-oxygen binding, such as carbon monoxide (CO) poisoning. Please see the corresponding section later in this chapter for further detail.

6.3 Physiologic Effects of Oxygen Breathing

6.3.1 Respiratory Effects

6.3.1.1 Breathing Control

Respiratory control is possible because of three key components: sensors, central control, and effectors (the muscles of respiration) (West 2000).

6.3.1.1.1 Sensors

Sensors include (1) central chemoreceptors, (2) peripheral chemoreceptors, and (3) pulmonary stretch receptors, each of which responds to changes in arterial oxygenation and inadequate ventilation.

1. *Central chemoreceptors* exist in the milieu of the brain's extracellular fluid and are located between the blood vessels and the cerebrospinal fluid (CSF). Carbon dioxide diffuses from the vasculature into the CSF,

thus decreasing pH. This decrease in CSF pH stimulates the central chemoreceptors to increase ventilation.

2. *Peripheral chemoreceptors* are located in the carotid bodies above and below the aortic arch. The carotid bodies are the most crucial element of the receptor system as they are responsible for an appropriate increase in ventilation in response to arterial hypoxemia. The response to changes in PCO_2 is a less important role of the peripheral chemoreceptors.
3. *Pulmonary stretch receptors*, a type of lung receptor, occur within airway smooth muscle. These receptors aid in decreasing respiratory frequency with lung distention. This is known as the Hering-Breuer reflex and is thought to be of greatest importance in newborn infants. Included within this group of receptors are the *irritant receptors* which lie between airway epithelial cells and are stimulated by noxious gases, such as cigarette smoke. This stimulus causes bronchoconstriction and hyperpnea. The *juxta-capillary* or *J-receptors* lie in the alveolar wall and are attributed to causing the rapid, shallow breathing exhibited in heart failure and interstitial lung disease.

6.3.1.1.2 Central Control

Central control of ventilation involves the brainstem as the primary mediator or triage center for the various types of input from the above-mentioned sensors. Central control begins in the cerebral cortex, which supports voluntary (corticospinal) breathing, and incorporates input from the brainstem which is involved with automatic (reticulospinal) breathing. These signals are then conducted to the anterior horn cells of the spinal cord and on to the motor neurons that supply the muscles of respiration. The motor neurons (in the cervicothoracic portion of the spinal cord) propagate these signals to the peripheral nerves and finally across the neuromuscular junctions leading to initiation of the respiratory muscles. Alterations with any part of this system, from the brainstem to the musculature, can result in respiratory insufficiency or failure.

6.3.1.1.3 Effectors (Respiratory Muscles)

Effectors are the muscles involved in ventilation including the diaphragm. Excess effector activity does provide negative feedback to the brainstem, which efficiently allows control of ventilation and oxygenation such that the PaCO_2 and PaO_2 levels are usually maintained within the normal range. The lower motor neurons propagate the incoming signal to the peripheral (or efferent) nerves supplying the muscles of respiration. The efferent nerves extend to the diaphragm, intercostals muscles, and the accessory muscles of the neck. These nerves divide into branches that reach the specific muscle fibers and apply themselves to the muscle membrane at the motor endplates. At these neuromuscular junctions, the chemical transmitter acetylcholine is released. Acetylcholine is responsible for depolarizing the muscle membrane, which results in the release of intracellular calcium, thus, initiating the contraction of the muscle fiber (Polkey and Moxham 2001). The muscles of respiration are divided into three main groups: (1) inspiratory muscles, (2) expiratory muscles, and (3) accessory muscles of respiration.

1. *Inspiratory muscles*: Inspiratory muscles provide outward forces and include our main inspiratory muscle, the diaphragm, which contributes almost three quarters of the inspiratory workload. Cervical nerves 3–5 supply the phrenic nerve, which controls the diaphragm. The external intercostal muscles provide additional inspiratory force, thus allowing elevation of the lower ribs and expansion of the rib cage during inspiration. They are innervated via the intercostal nerves, which derive from the thoracic spinal nerve roots.
2. *Expiratory muscles*: This group includes the internal intercostals which aid in expiration by passive relaxation. In addition, the abdominal muscles (internal obliques, external obliques, and transverse abdominus) help to reduce the thoracic volume by contracting to displace the diaphragm into the thoracic cavity. An additional contributor to this group, the rectus abdominus, helps to raise the pleural pressure during exhalation thus aiding in airflow out of the thorax.

3. *Accessory muscles of respiration*: This group includes the sternocleidomastoid, scalene, trapezii, latissimus dorsi, platysma, and pectoralis muscle groups. The accessory muscles contribute most prominently in situations associated with increased ventilatory demand, such as exercise, impending respiratory failure, and neuromuscular weakness. By contributing to rib cage expansion, these muscles support inspiration during active spontaneous breathing, though they may also add support during quiet breathing (Benditt 2006; Phillipson and Duffin 2005). The upper airways must maintain their patency throughout inspiration, and there is a corresponding increase in neural output to the pharyngeal wall muscles (genioglossus and arytenoid muscles) just prior to diaphragmatic contraction. Thus, the pharyngeal wall muscles are a crucial adjunct when the accessory muscles are in use.

6.3.1.1.4 Special Considerations for Infants

The infant's compliant chest wall and more circular thorax make the above respiratory processes less efficient. With increased inspiratory effort and diaphragmatic contraction, the lower ribs descend rather than elevate secondary to the compliant nature of the chest wall. The result is subcostal retractions and deformation of the chest wall rather than full lung expansion. Compared to older children and adults, infants are more likely to exhibit muscle fatigue due to the increased workload on the diaphragm. In addition, the diaphragm of infants has fewer type I muscle fibers which are slow-twitch, high-oxidative fibers inherently more resistant to fatigue. As children mature, the rib cage and diaphragm achieve a less horizontal position, and the quantity of type I fibers increases. These changes lead to increased generation of maximal inspiratory pressures and, hence, a less compliant chest wall.

6.3.1.2 Pulmonary Vasodilatation

Pulmonary vascular resistance (PVR) is predominantly determined by the diameter, length, and number of pulmonary vessels. The ability

to cause or allow pulmonary vasodilatation is dependent on the status and reactivity of the pulmonary vascular bed of each individual patient and may change within a given patient over time. The most important factor is the diameter of the pulmonary vessels, which is directly related to the vascular smooth muscle tone. In normal circumstances, minimal tone is present in the pulmonary circulation, and thus, pulmonary vascular resistance is low. Unlike the systemic vascular system, the pulmonary vasculature reacts to hypoxia with vasoconstriction. The exact mechanism is unknown but occurs when the alveolar PO_2 falls below approximately 50–60 mmHg. It should be noted that *alveolar* hypoxia is a more important factor in influencing PVR than pulmonary *arterial* hypoxia. This pulmonary vasoconstriction is an adaptive attempt to prevent flow of blood to hypoxic regions of the lung, thus improving ventilation-perfusion matching. The pulmonary arterial pH also affects the pulmonary vasculature in a manner opposite to what occurs systemically with acidosis causing pulmonary vasoconstriction. The prevention and treatment of metabolic acidosis help to limit any existing pulmonary hypertension. In addition, elevated levels of carbon dioxide in the blood increase PVR independent of an acidotic or alkalotic metabolic milieu.

6.3.1.2.1 Specific Therapies to Decrease PVR

Vasodilators are used to decrease pulmonary artery pressure (PAP) and to halt or reverse the vascular changes related to an elevated PVR.

Oxygen: From the perspective of the pulmonary vasculature, the purpose of optimal oxygen delivery is to reverse hypoxic pulmonary vasoconstriction. With chronic hypoxemia, supplemental oxygen is given to maintain a goal arterial oxygen saturation level of $\geq 90\%$ (Rubin and Rich 1997).

Nitric oxide (NO): Inhaled nitric oxide (iNO) is a potent, selective pulmonary vasodilator that acts to dilate the pulmonary vascular smooth muscle (endothelium) via cyclic GMP (guanosine monophosphate). Inhaled NO has a very short half-life of approximately 4 s and is synthesized from L-arginine by NO synthase. Nitric oxide

Table 6.1 Fraction of inspired oxygen by various delivery systems

Delivery system	FiO ₂ delivery (%)	Flow required (L)
Nasal cannula	24–50	<6
Simple face mask	<60	6–10
Venturi face mask or trach collar	<60	Variable
Partial rebreather face mask	<60	15
Non-rebreather face mask	~100	15

Adapted from: *Pediatric Critical Care Medicine*. Slonim AD, Pollack MM. 1st ed. Philadelphia, PA: Lippincott Williams & Wilkins. 2006. Adapted from Table 42.1. Page 717

is avidly bound to hemoglobin, so the intended effect is local. Impaired endogenous production of NO is intrinsic to the pathogenesis of pulmonary arterial hypertension. Inhaled NO via a ventilator circuit, face mask, or nasal cannula has been used clinically since the 1990s in the treatment of pulmonary hypertension. It has also been used diagnostically in the cardiac catheterization lab to determine pulmonary vasoreactivity. Inhaled NO lowers pulmonary artery pressure (PAP) in various disease states, including idiopathic pulmonary hypertension, congenital heart disease (CHD), and postoperative pulmonary hypertension (Atz et al. 2002) (Table 6.1). Rare side effects include systemic hypotension, methemoglobinemia, and excess generation of nitrogen dioxide (a highly reactive oxidant). The most significant risk of iNO is rebound pulmonary hypertension, which can occur when weaning a patient from iNO. There are data advocating a slow wean of iNO at doses less than 5 ppm. The addition of a single dose of sildenafil 1 h prior to discontinuing iNO therapy has been demonstrated to blunt the rebound effect (Namachivayam et al. 2006).

Nitroprusside and milrinone: Unfortunately, there is no intravenous (IV) pharmacologic agent that acts as a selective pulmonary vasodilator. The effect of various nonspecific IV vasoactive medications can have a variable relative effect on PVR. No IV vasodilator reliably decreases PVR more than SVR. When the patient requires left ventricular (LV) afterload reduction due to

decreased myocardial function, then a medication such as nitroprusside may have beneficial clinical value. Unfortunately, nitroprusside can cause systemic hypotension, thus lowering coronary perfusion pressure. Milrinone, a phosphodiesterase type-3 inhibitor in cardiac and smooth muscle, acts as an inotrope and vasodilator via an increase in cytoplasmic cyclic adenosine monophosphate (cAMP). Milrinone is used primarily in heart failure associated with congenital heart disease as well as for patients with cardiomyopathy. It is a nonspecific vasodilator and, thus, affects both PVR and SVR. Milrinone's long half-life often prevents its usage in patients with hypotension.

Intravenous prostacyclin (epoprostenol): An imbalance in the levels of prostacyclin exists in adults and children with severe pulmonary hypertension. Additionally, there is a decreased expression of prostacyclin synthase in the pulmonary vasculature. Prostacyclin (prostaglandin I₂) induces vascular smooth muscle relaxation via the production of cAMP. It is also an inhibitor of platelet aggregation. Epoprostenol has been approved for the treatment of pulmonary arterial hypertension since the 1990s. Long-term IV epoprostenol improves quality of life and survival in adults and children with primary pulmonary hypertension (Barst et al. 1999; Sitbon et al. 2002; Yung et al. 2004). Unfortunately, it must be administered as a continuous IV infusion via a central venous line secondary to its short half-life of 3 min. Clotting, hemorrhage, sepsis, and life-threatening cessation of IV infusion are all significant potential complications. Common and dose-related side effects include nausea, headache, flushing, diarrhea, musculoskeletal pain, and anorexia.

Inhaled prostacyclin (iloprost): Iloprost is a prostacyclin analogue delivered as aerosolized particles of 0.5–3 μm to ensure alveolar deposition and pulmonary selectivity. Inhaled prostacyclin has shown significant improvements in quality of life and symptoms in adults with pulmonary hypertension (Olschewski et al. 2002). Due to its half-life of only 25 min, it must be administered by inhalation at least 6–9 times a day for clinical effect. It allows selective

vasodilatation of the pulmonary vasculature with avoidance of central line complications. There are no data on chronic effects of inhaled prostacyclin in children, although it does appear to be a tolerable equivalent to IV prostacyclin. Side effects included headache, cough, dizziness, and systemic vasodilation. An additional potential side effect is lower airways obstruction, which can be potentially reversed with inhaled corticosteroid and β -agonist therapies (Ivy et al. 2008).

Phosphodiesterase-5 inhibitor (sildenafil): Sildenafil is an oral phosphodiesterase-5 inhibitor that prevents cGMP inactivation/breakdown, thus increasing the activity of endogenous NO at the level of vascular smooth muscle with resultant pulmonary vasodilatation. It is demonstrated to be as effective as iNO and may be useful in preventing rebound pulmonary hypertension during iNO weaning (Namachivayam et al. 2006; Schulze-Neick et al. 2003), in postoperative pulmonary hypertension (Atz et al. 2002; Schulze-Neick et al. 2003), and in pulmonary hypertension associated with chronic lung disease (Ghofrani et al. 2002).

Endothelin-receptor antagonist (bosentan): Endothelin-1 (ET-1) expression is increased in the pulmonary arteries of patients with pulmonary hypertension and causes direct vasoconstriction while stimulating the proliferation of vascular smooth muscle and contributing to fibrosis. ET-1 is a pro-inflammatory mediator produced by vascular endothelial and smooth muscle cells. Its activity is mediated by ET_A and ET_B receptors which are sites of potential modulation of the effects of ET-1. Bosentan, a dual ET-receptor antagonist, lowers PAP and PVR in adults and children with good overall tolerance. Bosentan may be used as a first-line agent in advanced pulmonary hypertension or in conjunction with other therapies, such as epoprostenol. Potential side effects include elevated hepatic transaminases, peripheral edema, systemic hypotension, and fatigue (Fig. 6.1).

6.3.1.3 Absorption Atelectasis

Atelectasis or “imperfect expansion” describes non-aerated but normal lung parenchyma.

Atelectasis can be secondary to intrinsic bronchial obstruction, mass effect from nearby structures, increased intrapleural pressure, abnormal alveolar surface tension, and neuromuscular disease. Absorption atelectasis describes a phenomenon which can occur with the inspiration of elevated concentrations of inspired oxygen (generally FiO₂ 1.0). Since the increase in venous PO₂ when breathing 100 % oxygen is only about 10–15 mmHg, the sum of the partial pressures in the alveolar gas mixture exceeds the partial pressures in the venous blood. Thus, gas can diffuse from the alveoli to the blood resulting in rapid collapse of the alveoli. Alveolar collapse is most likely to occur at the base of the lung, where the lung is least well expanded at baseline. Absorption collapse can also occur in regions of obstruction even when breathing room air, but the process is much slower. The rate of collapse is limited by the presence of N₂ which has a low solubility and acts as a “splint” supporting the alveoli and delaying collapse. Even small amounts of N₂ can provide this beneficial effect.

6.3.1.4 Pulmonary Oxygen Toxicity

Animal studies have demonstrated that exposure to FiO₂ 1.0 for even short periods of time results in damage to the alveolar epithelium with eventual replacement by type II alveolar cells. In addition, there is the loss of tight junctions in the alveolar capillary endothelium leading to increased permeability and hence pulmonary edema. Over time, interstitial fibrosis can develop. In humans, there is evidence of impaired gas exchange after only 30 h of inhalation of 100 % oxygen. Normal adult subjects who breathe FiO₂ 1.0 at atmospheric pressure for 24 h can develop respiratory distress and a significant decrease in vital capacity (VC) by 500–800 mL, likely due to absorption atelectasis (West 2000). Although there is no definite FiO₂ threshold associated with oxygen toxicity, most pediatric intensivists use a FiO₂ of 0.50–0.60 as an unacceptable oxygen level during prolonged mechanical ventilation. There is the additional danger of oxygen toxicity in premature infants with resultant retinal disease from local vasoconstriction of blood vessels behind the lens.

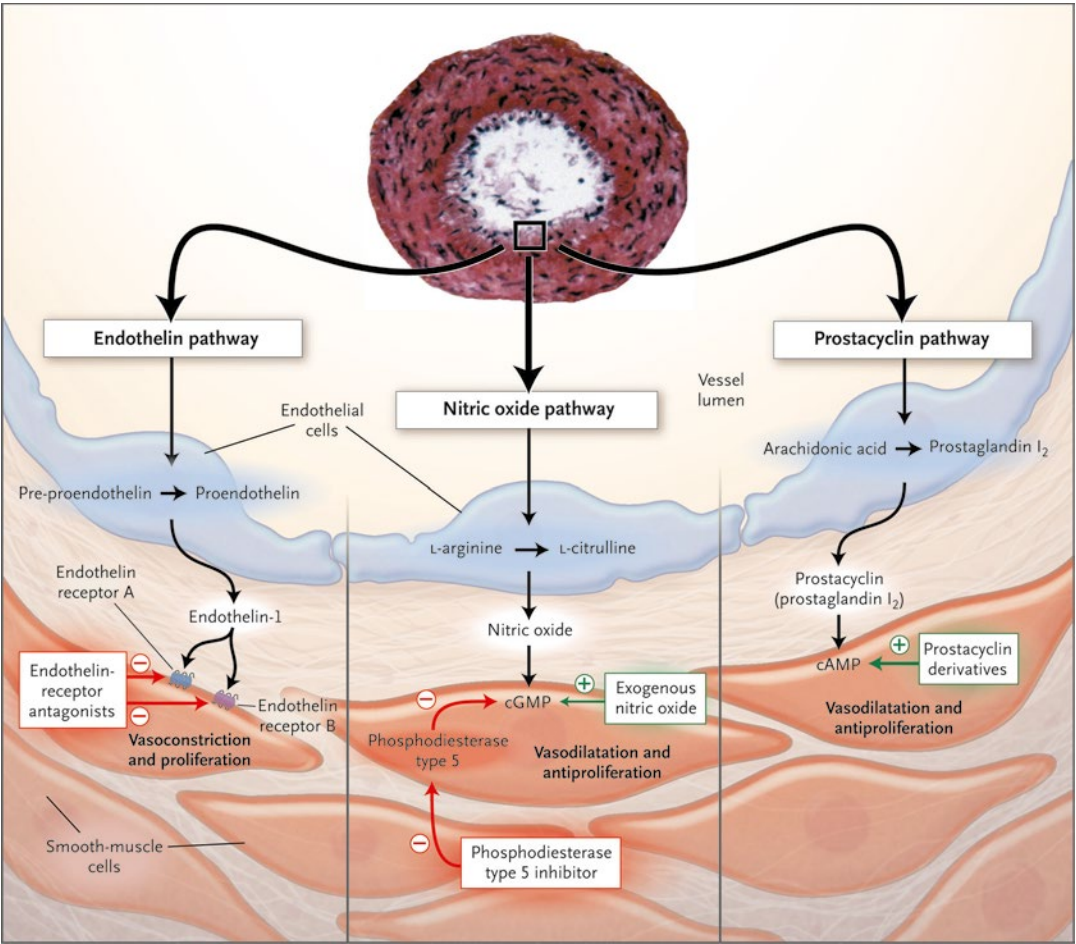


Fig. 6.1 Therapies to promote pulmonary vasodilatation: (Humbert et al. 2004)

This significant adverse effect can be avoided by lowering the acceptable PaO₂ levels. Please see Section 6.3 for further discussion.

6.3.2 Non-respiratory Effects of Oxygen

6.3.2.1 Hemodynamic Effects

The delivery of oxygen is a vital component of patient care within pediatric and neonatal intensive care units. Clinicians are constantly altering the support provided to each patient in an attempt to optimize global oxygen delivery as defined by the following equation:

$$DO_2 = CO \times \text{arterial } O_2 \text{ content}$$

$$\text{arterial } O_2 \text{ content} = \left(\begin{array}{l} \text{SaO}_2 \text{ saturation} \\ \times 1.39 (\text{mL/g}) \times \text{Hb} \\ + (0.003 \times \text{PaO}_2) \end{array} \right)$$

where DO₂ represents oxygen delivery; CO, cardiac output; SaO₂, arterial oxygen saturation; Hb, hemoglobin; and PaO₂, partial pressure of oxygen in arterial blood. Thus, decreased oxygen delivery can result from inadequate cardiac output, low arterial oxygen saturation level, inadequate hemoglobin concentration, and/or low PaO₂. Oxygen delivery to the tissues and organs of the body can be optimized by augmenting

cardiac output (via volume loading and/or vaso-active agents). Transfusion of packed red blood cells will augment oxygen delivery by increasing the arterial oxygen content; however, recent publications have raised increasing concerns over the use of transfusions in the critical care environment. Lastly, optimization of the oxygen delivery devices as discussed earlier in this chapter will lead to an increase in the arterial oxygen content and, thus, an increase in oxygen delivery to organs and tissues.

6.3.2.1.1 Response to Oxygen

An increase in PaCO_2 and/or a decrease in PaO_2 can cause an increase in ventilation. However, when PaCO_2 is within a normal range, the hypoxic stimulus to drive ventilation is blunted. In this circumstance, a PaO_2 of less than 50 mmHg is often required to elicit the appropriate ventilatory response. However, if the PaCO_2 is acutely elevated, a PaO_2 of less than 100 mmHg will be sufficient to elicit an increase in respiratory drive. In conditions with chronic CO_2 retention, such as bronchopulmonary dysplasia (BPD) and late-stage cystic fibrosis, arterial hypoxemia becomes the primary stimulus to ventilation. With chronic elevation of their CO_2 , these patients lose the stimulus to ventilate when exposed to increasing CO_2 levels. Their initial decrease in blood pH is buffered by renal compensation (HCO_3^- reabsorption), leaving little pH stimulation for the peripheral chemoreceptors. In these situations, arterial hypoxemia becomes the main stimulus to increase ventilation. Thus, delivering increased FiO_2 to such patients can result in significant hypoventilation and respiratory depression.

6.3.2.2 Oxygen Consumption

Traditional methods for measuring oxygen consumption, such as spirometry, preclude routine measurement in the neonatal and pediatric intensive care units. Advanced techniques with portable metabolic monitors and mass spectrometry are available. The metabolic monitors or “metabolic carts” use a gas-dilution principle to measure flow, a differential oxygen sensor for measuring change in oxygen concentration, and an infrared

carbon dioxide sensor. If we know the flow and differential concentrations, oxygen content can be calculated (Nichols 2008). Oxygen content in arterial and mixed venous blood is measured with co-oximetry techniques and a blood gas analyzer (PaO_2) using the following formula:

$$\begin{aligned} \text{O}_2 \text{ content (mL O}_2 \text{ / L blood)} \\ = [1.34 \times \text{Hb (g/L)} \times \% \text{saturation} / 100] \\ + [\text{PaO}_2 \text{ (mm Hg)} \times 0.003] \end{aligned}$$

where Hb represents hemoglobin.

6.3.2.3 Retinopathy of the Prematurely Born Infant (ROP)

ROP is characterized by the proliferative vascularization of the retina in preterm newborn infants. This disease is a major cause of visual impairment and sequelae in USA and Europe, including ametropias, strabismus and impaired color discrimination, or retinal detachment, resulting in decreased visual acuity (Phelps 1992). Prevention, actual screening recommendations, and novel treatment strategies decreased the incidence and improved the prognosis of ROP.

6.3.2.3.1 Pathophysiology

The retinal vessels develop between 16 weeks and 40 weeks of gestation. Vasculature of the retina is therefore incomplete and vulnerable in the premature newborn infant. An initial phase of ROP consists in microvascular obliteration causing a delay in the progression of the retina vessels from the center of optic disc towards the retinal periphery. The relative hyperoxia after birth mediates a decrease in the production of vascular endothelial growth factor (VEGF) and a vasoconstriction of the retinal capillaries. Ischemia of the retina triggers a compensatory neovascularization through upregulation of VEGF and IGF-1 expressions (Penn et al. 1994).

Neovascularization begins by 32–34 weeks postconceptional age. This proliferative retinopathy occurs at the junction between the vascularized and the avascular zone of the retina. Neovascularization leads to a fibrous scar

extending from the retina to the vitreous gel. Retraction of this scar tissue can cause retinal detachment.

6.3.2.3.2 Risk Factors

The main risk factors are prematurity, intra-uterine growth restriction, and exposure to supplemental oxygen (Darlow et al. 2005). Better monitoring of supplemental oxygen and decrease in baseline oxygen saturation have reduced the incidence of ROP (Sears et al. 2009). Recently, a large randomized study showed that a lower target range of oxygenation (85–89 %), as compared with a higher range (91–95 %), resulted in a significant decrease in severe retinopathy among survivors despite no change in the composite outcome of severe retinopathy or death (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network 2010). An increased magnitude and variability of fluctuations in oxygenation have been implicated in the development of ROP (Cunningham et al. 1995). Hypoxemic episodes during the first 8 weeks of life in preterm infants have been associated with severe ROP requiring laser therapy (Di Fiore et al. 2010). ROP has also been associated with prolonged mechanical ventilation, apnea, male sex, Caucasian race, sepsis, anemia, red blood cells transfusion, multiple gestations, and intraventricular hemorrhage (Darlow et al. 2005).

Furthermore, human and animal studies indicate that 70 % of the variance in susceptibility to ROP may be the result of genetic influences in the pathogenesis of ROP (Holmstrom et al. 2007).

6.3.2.3.3 Screening Guidelines

Systematic screening for ROP is recommended in infants less than 1,500 g or 30 weeks gestational age and selected infants with a birth weight between 1,500 and 2,000 g or a gestational age greater than 30 weeks at high risk for ROP (Section on Ophthalmology et al. 2006). The current benchmark is regular screening by indirect ophthalmoscopy until the retina is nearly or fully vascularized. Newborn infants less than 28 weeks gestation should be screened at 31 weeks post-

conceptional age. Newborn infants at or above 28 weeks gestation should be screened at 4 weeks after birth.

ROP is classified according to location, severity, and extent of the lesions. Five stages of ROP exist, ranging from stage 1 characterized by a demarcation line between vascularized and avascularized retina to stage 5 marked by a total retinal detachment. Plus disease is defined as venous dilation and arteriolar tortuosity in at least two quadrants of the posterior pole. Plus disease is the primary feature to indicate the necessity of treatment in high-risk ROP.

Digital imaging of the retina is currently used for sequential ROP screening (RetCam 120, Massie Research Laboratories, CA). Ocular imaging can be transmitted to distant specialized centers for analysis.

6.3.2.3.4 Current Treatments

Treatment of current ROP is based on peripheral retinal ablation by cryotherapy or laser photocoagulation (Good 2004; Hubbard 2008). Advances in treatments are being investigated with better knowledge on the pathogenesis of ROP, including factors regulating VEGF and IGF-1 production. Hence, monoclonal antibody directed against VEGF has been used in combination or not to laser photocoagulation in severe ROP. Injection of VEGF antibody has been associated with regression of retinal proliferation within days (Kong et al. 2008). The role of omega-3-polyunsaturated fatty acids in the prevention of ROP is being currently studied. Experimental studies in mouse showed that elevation of omega-3-PUFA content was protective against neovascularization (Connor et al. 2007). Additional omega-3-polyunsaturated fatty acids intake may be of benefit in preventing retinopathy.

6.3.3 Hyperbaric Oxygen Therapy (HBO)

During hyperbaric oxygen therapy, a patient is placed in a treatment chamber where he or she breathes 100 % oxygen as the pressure of the chamber is increased to greater than 1 atm.

When the inspired oxygen is increased to 3 atm in a hyperbaric chamber, the amount of dissolved O_2 in arterial blood increases from 1.5 mL/dL to 6 mL/dL, and O_2 tension in tissues is increased to nearly 400 mmHg. In this altered environment, O_2 has various biochemical, cellular, and physiologic benefits as described below. HBO therapy is indicated for use in carbon monoxide (CO) poisoning, myonecrosis, necrotizing fasciitis (gas gangrene of soft tissues), arterial air emboli, and decompression sickness.

6.3.3.1 CO Poisoning

Hemoglobin has 240 times the affinity for CO than oxygen. Once bound, carboxyhemoglobin (COHb) shifts the oxyhemoglobin curve to the left leading to decreased oxygen-carrying capacity. CO also binds to cytochrome oxidase, interfering with electron transport and adenosine triphosphate (ATP) production with resultant cellular dysfunction. In CO poisoning, the patient's arterial oxygen content (PaO_2) is often normal or elevated, and routine pulse oximetry measurements can be falsely normal since most technologies do not differentiate between oxyhemoglobin and carboxyhemoglobin. In general, co-oximetry is required to quantify COHb concentration. The most important therapeutic intervention is administration of 100 % oxygen after removing the patient from the carbon monoxide source. Only very high PaO_2 levels can compete with CO for Hb binding, thus driving CO out of the blood. At 3 atm of pressure in an HBO chamber, the half-life of COHb is reduced from 5.3 h to just 23 min. However, the COHb level is not reflective of the severity of illness, and patients should be treated based on presence of symptoms, especially neurologic abnormalities. Referral to a facility with hyperbaric oxygen (HBO) capabilities is recommended for concerning clinical signs such as seizures, altered mental status, syncope, chest pain, severe acidosis, pregnancy. The risk of fatality is high with levels over 70 %. However, it must be noted that no consistent dose response relationship has been demonstrated between carboxyhemoglobin level and clinical effect.

6.3.3.2 Wound Healing

Since HBO increases the capillary-tissue oxygen gradient, this likely explains potential benefits that have been seen in wound healing. HBO helps to promote angiogenesis and can help restore neutrophil-mediated bacterial killing. HBO is also helpful in treating *gas gangrene* as the organisms cannot survive in such a high PO_2 environment.

6.3.3.3 Air Emboli

Based on Boyle's law, gas volume is inversely proportional to pressure. Therefore, the "bubble volume" in cases of air emboli and decompression sickness is reduced within the highly pressurized HBO chamber, helping to relieve small vessel obstruction and restore blood flow to compromised tissue beds.

6.3.3.4 Toxicity/Complications

Complications of HBO can include seizures, gas embolization, pneumomediastinum, pneumothorax, perforated tympanic membranes, and oxygen toxicity (reversible myopia, decreased pulmonary compliance). Extreme care must be taken to avoid fires and explosions at such high partial pressures of oxygen.

Essentials to Remember

- The most important factor in determining if an oxygen gas delivery system is sufficient to meet a patient's inspiratory demand is the gas flow rate.
- The three key components of respiratory control are sensors, central control, and effectors (muscles of respiration).
- Pulmonary vasodilators decrease pulmonary artery pressure and can halt or reverse the vascular changes related to elevated pulmonary vascular resistance.
- Decreased oxygen delivery to the organs and tissues of the body results from inadequate cardiac output, low arterial oxygen saturation level, inadequate hemoglobin concentration, or low PaO_2 .

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Nasal CPAP: An Evidence-Based Assessment

7

Sherry E. Courtney

Education Aims

- To understand and describe the different NCPAP devices
- To explain the current evidence regarding advantages of NCPAP use in infants
- To describe potential complications of NCPAP use

Nasal continuous positive airway pressure (NCPAP) has become extremely popular over the past few years. Though its use is based in strong physiologic principles, more data as to the beneficial short- and long-term effects as well as possible complications are still needed. Personal opinions and biases have played a role in this arena as well. In this chapter, we will describe the major ways to provide NCPAP that are currently employed as of this writing. We will then discuss the studies of NCPAP that have been done to date and classify them according to level of evidence. Finally, we will draw some conclusions based on the evidence presented and suggest areas for future investigation.

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7.1 History of NCPAP

Though NCPAP was described for use in neonates a century ago (Von Reuss English translation 1921), it was not implemented with any regularity until the 1970s, after the description of its use by Gregory et al. in a 1971 *New England Journal of Medicine* report (Gregory et al. 1971). Neonatology was a growing new subspecialty at that time and respiratory distress syndrome (RDS) and its treatment of utmost interest. A few years earlier, Avery and Meade had shown RDS to be due to surfactant deficiency (Avery and Mead 1959), but treatment remained largely only the use of supplemental oxygen. The death of President Kennedy's son Patrick from RDS at a gestational age of 34 weeks, in 1963, occurred prior to use of mechanical ventilation in newborn infants. Even after mechanical ventilation became more commonplace, end-expiratory pressure was not routinely used.

Use of nasal prongs to provide NCPAP was described by Kattwinkel et al. in 1973 (Kattwinkel et al. 1973). However, prongs were seldom used at that time, and respiratory support generally was provided with a ventilator via an endotracheal tube. It was commonly believed in the 1970s and much of the 1980s that premature infants should remain on the ventilator until "big enough" to be entirely self-sufficient with no need for any respiratory support.

Bronchopulmonary dysplasia (BPD) emerged as an important cause of morbidity and mortality once infants' lives could be prolonged with mechanical ventilation. During the 1980s, intense interest in ways to improve pulmonary outcome led to trials of exogenous surfactant and alternative approaches to ventilation, such as high-frequency oscillation. Use of NCPAP as a primary or even secondary mode of respiratory support waned considerably. In the late 1980s, interest in NCPAP revived due to a report of less BPD at Babies and Children's Hospital, Columbia University, in New York City (Avery et al. 1987). Recent randomized trials do not show an increase in BPD when early NCPAP is compared to early intubation, and a recent meta-analysis concludes that early NCPAP with selective surfactant therapy decreases death or BPD compared to prophylactic surfactant (Rojas-Reyes 2012). Since then, interest in providing respiratory support without the need for an endotracheal tube has remained high.

7.2 Description of NCPAP Devices

7.2.1 Continuous Flow

Continuous-flow NCPAP devices change CPAP pressure predominantly by a mechanism other than a change in flow. The best example is ventilator-generated CPAP. Flow remains constant, while pressure is adjusted by changes in resistance at the expiratory valve mechanism of the ventilator circuit. Bubble CPAP is essentially a continuous-flow device as well, since CPAP pressure is controlled mainly by the underwater depth of the expiratory tubing (Fig. 7.1). Flow does contribute to pressure change during bubble CPAP, however, and accurate monitoring of pressure at the nares is necessary to assure the appropriate pressure is being delivered (Kahn et al. 2007, 2008). A variety of prongs can be used to deliver continuous-flow NCPAP;

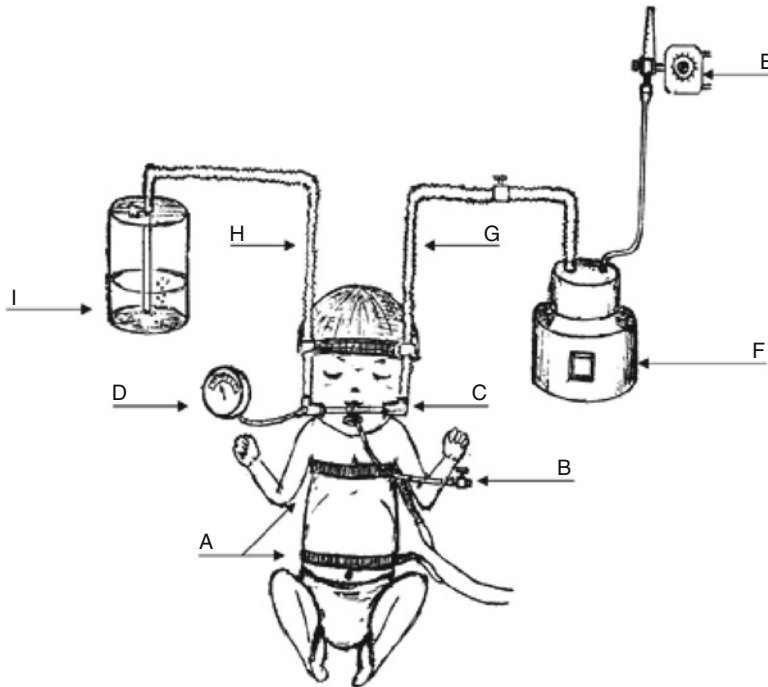


Fig. 7.1 Bubble NCPAP. (A) Respiratory inductance plethysmography abdominal and chest bands; (B) esophageal balloon connected to pressure transducer. (A, B) are being used for pulmonary mechanics measurements in this case. (C) Nasal prongs, (D) manometer, (E) oxygen

blender with flowmeter, (F) heated humidifier, (G) inspiratory tubing, (H) expiratory tubing, (I) underwater bubble chamber (J Perinatology 2005 vol 25 p. 454, with permission)

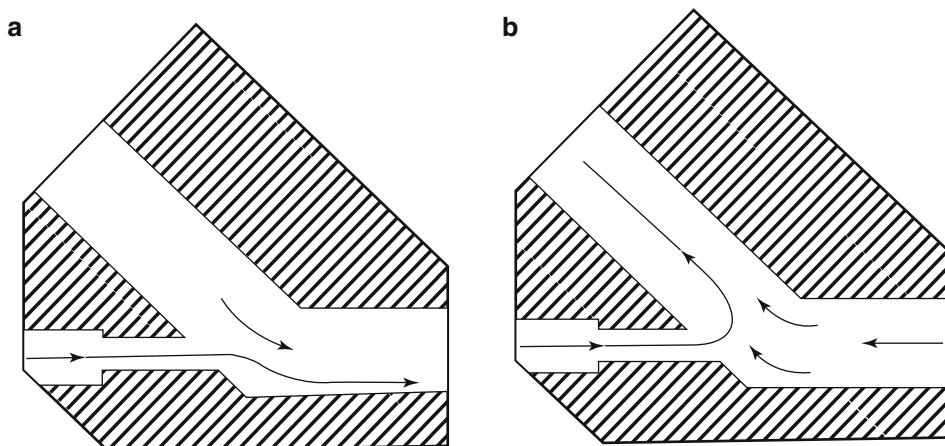


Fig. 7.2 Variable-flow NCPAP generator. (a) Inhalation: jet towards inspiratory branch. (b) Exhalation: jet flow diverted down expiratory branch (Neonatal Intensive Care vol 13 #5 Sep 2000, with permission)

Fig. 7.3 Infant Flow NCPAP generator applied to an infant model (With permission, CareFusion, Inc.)



most are binasal prongs, which appear to be more effective than use of a single prong (De Paoli et al. 2008).

7.2.2 Variable Flow

Variable-flow NCPAP devices change CPAP pressure by adjustments in the flow rate. Variable-flow devices are for the most part freestanding machines that employ a special nosepiece. The nosepiece acts to stabilize mean airway pressure by entraining gas at the inspiratory jets

and reduce work of breathing by the Coanda effect, whereby exhalation “flips” the inspiratory gas flow along the path of least resistance – the curved surface of the expiratory pathway (Moa et al. 1988; Pandit et al. 2001) (Fig. 7.2). As of this writing the most commonly employed variable-flow device is the Infant Flow[®] system (CareFusion, Inc., Yorba Linda, CA) (Fig. 7.3); another very similar device is the Arabella[®] (Hamilton Medical, Reno, NV). The Benveniste gas-jet valve CPAP device is used predominantly in Scandinavia and is essentially a variable-flow CPAP (Benveniste et al. 1976). The device



Fig. 7.4 Bi-level NCPAP device (SiPAP, with permission, CareFusion, Inc.)

consists of a straight nozzle and a curved tube that are positioned coaxially with a ring. CPAP level is changed by increasing or decreasing flow. Pressure generated should be measured with an accurate manometer.

7.2.3 Bi-level CPAP

Bi-level CPAP provides CPAP at two levels instead of one. The device cycles between levels with a rate and time at the higher level that are operator dependent. The bi-level device available at this writing is SiPAP® (CareFusion, Inc., Yorba Linda, CA) (Fig. 7.4), which functions in the same way as the Infant Flow® system and uses the same special nosepiece. The SiPAP-TR®,

available outside of the USA, can be equipped with a Graseby capsule for synchronization of the initiation of the higher CPAP level with the infant’s breathing.

7.2.4 Nasal Intermittent Positive Pressure Ventilation (NIPPV)

NIPPV uses a non-intubated NCPAP device to provide positive pressure ventilation. NIPPV is discussed elsewhere in this book and will not be included in this chapter.

7.3 Assessing the NCPAP Data

Studies of NCPAP have been varied, extend back over many years, and include a variety of study designs. Additionally, NCPAP is employed using a variety of devices and under a variety of circumstances. It is thus extremely difficult to assess the existing NCPAP studies. We will attempt to do so by discussing the following somewhat arbitrary but nonetheless useful general categories of studies:

- 1. NCPAP used at resuscitation (surfactant not part of the study group assignment)
- 2. NCPAP used early or prophylactically for respiratory distress (surfactant again not part of the study group assignment)
- 3. NCPAP used in conjunction with exogenous surfactant
- 4. NCPAP used for extubation
- 5. NCPAP used for apnea of prematurity
- 6. Comparison of NCPAP devices

To provide an evidence-based approach to assessing the NCPAP data in these categories, we will use the following classification of evidence:

1. Level I	Systematic review of randomized controlled trials
2. Level II	Randomized controlled trial
3. Level III	Cohort study
4. Level IV	Case-control study
5. Level V	Case series or historical controls
6. Level VI	Studies completed prior to 1990

The inclusion of Level VI, studies completed prior to 1990, is important for respiratory therapies in neonates, as in 1990 exogenous surfactant use was approved by the FDA and its use became commonplace. Exogenous surfactant had a dramatic effect on morbidity and mortality of the preterm infant. About this time, as well, began dramatic differences in how infants were ventilated, including high-frequency oscillatory and jet ventilation, synchronized conventional ventilation, and attention to prevention of volutrauma and barotrauma. Additionally, use of antenatal steroids became more common. Studies done prior to this time may not be relevant to today.

We also will not discuss every article ever published on the topic of NCPAP. Articles included in meta-analysis will in general not be individually discussed. We hope nonetheless to present the articles that will be most helpful and representative of the current literature as of this writing and that this approach will give the reader an idea of the state of the art regarding NCPAP in neonates. Also, in the following Tables, note that “Favors” will imply that some benefit was found.

7.3.1 NCPAP Used at Resuscitation

There is no question that a well-done meta-analysis of randomized controlled trials is usually the highest level of available evidence. However, there are several mitigating factors, including the publication dates of included trials. Several Cochrane reviews of NCPAP use have been published, but many are of limited value today due to inclusion of trials done in the 1970s and 1980s.

Use of positive pressure during resuscitation makes good physiologic sense, as fluid must be absorbed from the alveolar space and alveolar units that may be atelectatic must be opened. Yet until very recently no randomized trials addressed this topic. Use of positive end-expiratory pressure (PEEP) during positive pressure ventilation at resuscitation still has not been sufficiently studied, even today (O'Donnell et al. 2004). Upton and Milner reported a case series of 30 babies studied in the late 1980s and suggested that use of positive end-expiratory pressure (PEEP) during

resuscitation might be useful in establishing functional residual capacity (FRC) (Upton and Milner 1991). Lindner et al. reported a retrospective cohort study with historical controls, comparing immediate intubation (control, 1994, $n=56$) with immediate NCPAP (1996, $n=67$) in extremely low birth weight (ELBW) infants. They found a reduction in need for intubation in the latter group (25 %) (Lindner et al. 1999).

Several more recent studies are of note. In 2004, Finer et al. reported a study of 104 ELBW infants randomized to receive either CPAP/PEEP or not, using a neonatal T-piece resuscitator (NeoPuff Infant Resuscitator, Fisher-Paykel, Auckland, New Zealand). In this pilot study, CPAP/PEEP in the delivery room did not affect the need for intubation, either in the delivery room or in the NICU (Finer et al. 2004). In a study reported in 2007, te Pas and Walther described a randomized trial of 207 infants <33 weeks gestation. Infants received either bag and mask ventilation with minimal PEEP or a sustained inflation then NCPAP, using the NeoPuff. These infants were considerably larger than those reported by Finer (mean birth weight about 1,300 g vs. about 775 g). In these larger infants, 37 % of the NCPAP babies required intubation by 72 h and 51 % of the bag- and mask-ventilated babies ($p=0.04$) (te Pas and Walther 2007).

In a large multicenter study, Morley et al. randomized 610 infants of from 25 to 28 weeks gestation to CPAP or intubation at 5 min of life. At 28 days, fewer infants were on oxygen and fewer infants required ventilation in the CPAP group. However, the rate of death or BPD at 36 weeks did not differ between groups, and the incidence of pneumothoraces in the CPAP group was 9 % vs. 3 % in the intubation group (Morley et al. 2008).

Tapia et al. studied 256 infants who weighed 800–1500 g and were breathing spontaneously at birth. Infants were randomized to NCPAP or oxyhood/nasal cannula; subsequent surfactant was given according to preset criteria. Those in the NCPAP group were returned to NCPAP after surfactant, the others were continued on mechanical ventilation. Those in the NCPAP group had reduced need for surfactant therapy and mechanical ventilation.

Summary Table: resuscitation

Study	Level of evidence	Favors CPAP	Neutral	Favors alternative
Upton and Milner (1991)	V	X		
Lindner et al. (1999)	III	X		
Finer et al. (2004)	II		X	
te Pas and Walther (2007)	II	X		
Morley et al. (2008)	II		X	
Tapia et al. (2012)	II	X		

7.3.2 NCPAP Used Early or Prophylactically for Respiratory Distress

The meta-analysis by Ho et al. of early CPAP vs. delayed CPAP includes only studies completed prior to 1990 (Ho et al. 2010). Thus, though the analysis found subsequent use of mechanical ventilation was reduced with early CPAP, the relevance of this finding to current practice is unknown and we will consider this analysis to be of historical interest (Level VI evidence). Avery et al., in a cohort study of eight centers published in 1987, found a decrease in BPD in one center that used early NCPAP (Avery et al. 1987). In another cohort trial including the years 1988–1993, Jonsson et al. found that only one-third of infants treated with early NCPAP subsequently required mechanical ventilation (Jonsson et al. 1997).

A 2005 meta-analysis by Subramaniam et al. assesses the similar question of prophylactic NCPAP, prior to any signs of respiratory distress. The authors conclude there is insufficient evidence to address this question (Subramaniam et al. 2005). Only two trials are included, one of

which was completed prior to 1990. The other trial, published by Sandri et al. in 2004, found no benefit to prophylactic NCPAP (Sandri et al. 2004). The primary endpoint in this trial was the need for exogenous surfactant.

In 2008, Ho et al. updated their meta-analysis on CPAP for respiratory distress and included continuous negative extrathoracic pressure (CNEP) as well as positive pressure. Again, most of the studies were published well prior to 1990, though two of the included studies were completed after 1990. Buckmaster et al. randomly assigned 300 infants, all >30 weeks gestation and at non-tertiary centers, to either NCPAP or oxygen by headbox. Fewer infants on NCPAP required transfer or failed therapy; more NCPAP infants suffered pneumothorax (Buckmaster et al. 2007). The second trial, by Samuels et al., evaluated CNEP vs. headbox oxygen. Surviving infants on CNEP required fewer days on oxygen, 20.5 vs. 38.9. Mortality was not significantly different (Samuels et al. 1996). The meta-analysis, which includes the studies by Buckmaster and Samuels, concluded that continuous distending pressure reduces respiratory failure and mortality, but increases pneumothorax (Ho et al. 2008).

Summary Table: early or prophylactic use

Study	Level of evidence	Favors CPAP	Neutral	Favors alternative
Ho et al. (2010)	VI	X		
Avery et al. (1987)	VI	X		
Jonsson et al. (1997)	III/VI	X		
Subramaniam et al. (2005)	I/VI		X	
Ho et al. (2008)	I/VI	X		

7.3.3 NCPAP Used in Conjunction with Exogenous Surfactant

Interest in early NCPAP use combined with selective surfactant administration as a way to avoid prolonged mechanical ventilation has resulted in multiple recent studies and meta-analyses. In 1994 Verder et al. reported a study in which 68 infants were randomized to either NCPAP+surfactant, or NCPAP alone (Verder et al. 1994). Surfactant was given by what has come to be known as the INSURE technique (INtubate, give SURfactant, and Extubate). The infants were larger than in most subsequent studies, with mean birth weight of >1300 g. The authors found that infants in the NCPAP+surfactant group had reduced need for mechanical ventilation (MV) (43 % vs 85 %; $p=0.003$). In a study of 60 much smaller and more immature infants, mean birth weight of about 950 g, Verder et al. examined whether infants requiring NCPAP would fare better with early surfactant therapy (oxygen requirements 37–55 %) or later treatment (oxygen requirements 57–77 %). Infants in the early treatment group had a greatly reduced incidence of death or need for mechanical ventilation (21 % vs. 63 %) (Verder et al. 1999).

Tooley and Dyke randomized 42 infants of 25–28 weeks gestation to early surfactant and extubation to NCPAP vs. early surfactant and MV. By 72 h of age, significantly fewer infants were intubated in the NCPAP group (47 % vs. 81 %) (Tooley and Dyke 2003).

A meta-analysis addressing the question of early surfactant followed by NCPAP vs. continued MV was published in updated form by Stevens et al. in 2007. These reviewers concluded that early exogenous surfactant with extubation to NCPAP, when compared to later, selective exogenous surfactant use with continued MV, is associated with less MV need, lower BPD incidence, and fewer air leaks (Stevens et al. 2007).

Kribs et al. reported in an observational study several cohorts of infants treated from 2000 to 2004. During this time, early NCPAP and early surfactant therapy use became more and more

common, and in addition survival increased and BPD rates decreased (Kribbs et al. 2008).

A large study from Columbia by Rojas et al. was reported in 2009. In this randomized trial 279 infants born between 27 and 31 weeks gestation and with evidence of respiratory distress were randomly assigned to early NCPAP/surfactant or NCPAP alone. The primary outcome was the need for subsequent mechanical ventilation. Criteria for MV were predefined. The need for MV was 26 % in the NCPAP/surfactant group vs. 39 % in the NCPAP group (RR=0.69; 95 % CI 0.49–0.97). Additionally, air leak was less in the NCPAP/surfactant group (2 % vs. 9 %; RR=0.25; 95 % CI 0.07–0.85) (Rojas et al. 2009).

Several recent studies have addressed whether prophylactic surfactant is superior to NCPAP with a selective administration of surfactant. In 2009, Sandri et al. reported a randomized comparison of these interventions in 208 infants between 25–28 weeks' gestation. No differences in need for MV, death, or major morbidities were found between groups (Sandri et al. 2009). In the largest study to date, the SUPPORT Study Group performed a randomized, multicenter trial using a factorial design to assess early CPAP (delivery room) vs. intubation/surfactant (within 1 h of birth) and target ranges of oxygen saturation in extremely preterm infants (those born between 24 weeks 0 days and 27 weeks 6 days). A total of 1,316 infants were enrolled. Death or BPD (defined as oxygen requirement at 36 weeks) was not different between groups. Some secondary outcomes favored the NCPAP group: requirement for intubation, postnatal use of corticosteroids for BPD, days of mechanical ventilation, and mechanical ventilation by day 7 (SUPPORT Study Group 2010).

The Vermont Oxford Network studied three initial management strategies in infants from 26 0/7 to 29 6/7 weeks: prophylactic surfactant followed by mechanical ventilation, prophylactic surfactant with extubation to NCPAP, and initial NCPAP with selective administration of surfactant (Dunn et al. 2011). This study enrolled 648 infants but closed prior to attaining the required sample size of 876. No differences in the primary outcome measure of death or BPD were found,

but fewer infants in the NCPAP group required intubation or surfactant.

None of the above studies found a reduction in BPD with use of NCPAP. However, two things are important to note: one, no study has found an increase in BPD with NCPAP/selective surfactant;

and two, a recent meta-analysis has found that in studies with routine application of NCPAP, the combined outcome variable of death/BPD favors early NCPAP with selective surfactant use over prophylactic surfactant (RR=1.12; 95 % CI 1.02–1.24) (Rojas-Reyes et al. 2012).

Summary Table: use of NCPAP plus surfactant

Study	Level of evidence	Favors CPAP +early surf	Neutral	Favors CPAP alone, MV, or late surf
Verder et al. (1994)	II	X		
Verder et al. (1999)	II	X		
Tooley and Dyke (2003)	II	X		
Stevens et al. (2007)	I	X		
Kribbs et al. (2008)	III	X		
Rojas et al. (2009)	II	X		
Sandri et al. (2010)	II		X	
SUPPORT (2010)	II	X		
Dunn et al. (2011)	II	X		
Rojas-Reyes et al. (2012)	I	X		

7.3.4 NCPAP for Extubation

Davis and Henderson-Smart reported a meta-analysis of NCPAP following extubation. Eight of the nine included trials were published after 1990 (Davis and Henderson-Smart 2003). The conclusion of this meta-analysis (assessed as up to date in 2009) was that NCPAP is in fact effective in preventing failure of extubation in preterm infants.

One study, by Robertson and Hamilton, was not included in the meta-analysis because of a somewhat different study design, assessing NCPAP with a weaning regimen if tolerated compared to hood oxygen with an escalation regimen if needed. In this randomized study of 58 infants between 24 and 32 weeks gestation, no differences in extubation success were noted (Robertson and Hamilton 1998).

Summary Table: NCPAP for extubation

Study	Level of evidence	Favors CPAP	Neutral	Favors alternative
Robertson and Hamilton (1998)	II		X	
Davis and Henderson-Smart (2003)	I	X		

7.3.5 NCPAP Used for Apnea

NCPAP is often used for treatment of apnea of prematurity, despite relatively little data on this topic. Most studies are quite small and were done many years ago. A meta-analysis of CPAP vs. theophylline for apnea of prematurity was published in 2001 by Henderson-Smart and Davis and updated as current in 2005 (Henderson-Smart et al. 2001). It included only one study, concluded prior to 1990. In this study, CPAP was

applied using a face mask, and theophylline was more effective.

In 1975 Kattwinkel et al. studied 18 preterm infants and found apnea was reduced by 69 % with NCPAP and only by 39 % with prophylactic cutaneous stimulation (Kattwinkel et al. 1975).

In 1976, Speidel and Dunn reported 5 preterm infants who had reduced or abolished apnea with application of CPAP (Speidel and Dunn 1976). In 1985, Miller et al. described 14 preterm infants with and without CPAP and found both mixed

and obstructive apnea to be decreased with CPAP (Miller et al. 1985). Central apnea was not affected. These investigators, in 1990, reported decreases in supraglottic resistance in 10 preterm

infants studied on CPAP and postulated that apnea may be reduced by a mechanical splinting of the airway (Miller et al. 1990). Clearly more investigation is needed in this area.

Summary Table: NCPAP for apnea of prematurity

Study	Level of evidence	Favors CPAP	Neutral	Favors alternative
Kattwinkel et al. (1975)	VI	X		
Speidel and Dunn (1976)	VI	X		
Miller et al. (1985)	VI	X		
Miller et al. (1990)	V	X		
Henderson-Smart et al. (2001)	VI			X

7.4 Comparative Studies of NCPAP Devices

7.4.1 Infant Studies

There are a variety of NCPAP devices/pressure sources available, as we have previously discussed. As briefly mentioned at the beginning of this chapter, an updated Cochrane meta-analysis was published by De Paoli et al. (2008). The review included randomized studies of infants either treated early with NCPAP or extubated to NCPAP. The reviewers concluded that short binasal prongs are more effective than single prongs when assessing rates of re-intubation and more effective than nasopharyngeal prongs for RDS. The Infant Flow system (variable flow) appears to be more effective than standard short binasal prongs for some outcomes. Length of stay and days on oxygen were less with variable-flow NCPAP in one study (Stefanescu et al. 2003) and re-intubation was less in another study only published in abstract form.

Ahluwalia et al. evaluated 20 infants in a crossover study of single-prong NCPAP and variable flow. There were no short-term differences in FiO₂ or vital signs (Ahluwalia et al. 1998). In a non-randomized study, Kavvadia et al. evaluated the same devices and found no short-term advantage of variable flow (Kavvadia et al. 2000).

In 2001, Courtney et al. reported greater lung volume recruitment with variable flow vs. con-

tinuous flow or cannula (Courtney et al. 2001), and Pandit et al. reported a decreased work of breathing with variable flow compared to continuous-flow NCPAP (Pandit et al. 2001). Liptsen et al. have described more asynchronous breathing with bubble NCPAP compared to variable flow (Liptsen et al. 2005), and Boumecid et al. reported increased tidal volume and thoracoabdominal synchrony with variable flow compared to continuous flow or nasal cannula (Boumecid et al. 2007). Variable-flow vs constant flow NCPAP was assessed in a multi-center randomized trial of 276 Polish infants of birth weight 750–1500 g. There were no differences in the need for intubation or reintubation between groups (Bober et al. 2013).

Gupta et al. randomized 140 infants of 24–29 weeks gestation to either bubble NCPAP or variable flow and found no differences in successful extubation. A subgroup analysis found lower extubation failure rates with bubble NCPAP (Gupta et al. 2009). No other large randomized trials of bubble CPAP assessing clinical outcomes have been done. A randomized crossover study by Courtney et al. assessing work of breathing and other respiratory parameters between bubble and ventilator-derived NCPAP found no differences in most outcomes, but a higher transcutaneous PO₂ during bubble NCPAP (Courtney et al. 2010).

Bi-level NCPAP has not been well studied either, but studies to date are encouraging. In a crossover study of variable-flow NCPAP vs. variable-flow BiPAP, Migliori et al. found better

oxygenation and ventilation with bi-level NCPAP (Migliori et al. 2005). Lista et al. randomized 40 infants to either variable-flow NCPAP or bi-level NCPAP. Infants in the bi-level group had a shorter period of respiratory support, fewer days on oxygen, and a decreased length of stay (Lista et al. 2010). O'Brien et al. reported no difference in extubation success in 136 infants less than or equal to 1250 g, randomized to either bi-level or continuous NCPAP. This study was terminated at fifty percent necessary sample size, however (O'Brien et al. 2013).

Since most nasal cannula systems cannot monitor the pressure delivered, it is difficult to directly compare cannula use with NCPAP. It is important to note, however, that cannulas can deliver significant positive pressure, as noted by Locke et al. in 1993 (Locke et al. 1993). Courtney et al. and Sreenan et al. confirmed this in 2001 (Courtney et al. 2001; Sreenan et al. 2001). Kubicka et al. measured oral cavity pressures during cannula treatment in 27 infants and noted significant unpredictability in the levels of CPAP achieved (Kubicka et al. 2008). High-flow nasal cannulas are discussed in sect. 7.5.

Summary Table: NCPAP devices (not all devices compared in each study)

Study	Level of evidence	Favors standard CF or bubble	Favors VF	Favors Bi-Level	Favors single prong	Favors double prongs	ND
Ahluwalia et al. (1998)	II						X
Kavvadia et al. (2000)	V						X
Courtney et al. (2001)	II		X				
Pandit et al. (2001)	II		X				
Stefanescu et al. (2003)	II		X				
Liptsen et al. (2005)	II		X				
Migliori et al. (2005)	III			X			
Boumeced et al. (2007)	II						
De Paoli et al. (2008)	I		X				
Gupta et al. (2009)	II	X					
Lista (2010)	II			X			
Courtney et al. (2010)	II	X					
Bober et al. (2013)	II						X
O'Brien (2013)	II						X

CF continuous flow, VF variable flow, ND no difference

7.4.2 Model and Animal Studies

Several interesting model studies and animal studies of NCPAP have been conducted. In 1996, Klausner et al. compared work of breathing (WOB) during variable flow vs. continuous-flow NCPAP in a model and found WOB to be decreased with variable flow, a fact later confirmed in infants by Pandit et al. (Klausner et al. 1996; Pandit et al. 2001).

Using a calibrated pressure transducer, De Paoli et al. compared resistance to airflow using a variety of NCPAP prongs. Devices with short double prongs had the lowest resistance to airflow, with medium and large size Infant Flow prongs actually creating a negative pressure

within the variable-flow device (De Paoli et al. 2002).

Pillow et al. have studied bubble NCPAP in the intubated lamb model and found that compared to standard continuous-flow NCPAP, blood gases and ventilation inhomogeneity were improved and alveolar protein decreased with bubble NCPAP (Pillow et al. 2007). Whether this applies to the unintubated animal is not known. Kahn et al. compared bubble NCPAP and standard continuous-flow NCPAP in a model study and found that flow significantly influences the delivered pressure during bubble NCPAP, with increasing flow causing significant increases in the delivered pressure (Kahn et al. 2007). These investigators subsequently confirmed this finding

in a group of preterm infants (Kahn et al. 2008). Based on their findings, they recommend accurate monitoring of the pressure delivered to the nares during bubble NCPAP.

Thomson et al., in a baboon model, found that early extubation of the preterm baboon to NCPAP did not cause arrested alveolar development, and lungs were similar to more mature preterm baboon lungs (Thomson et al. 2004).

7.5 High-flow Nasal Cannula

For many years clinicians have weaned infants from NCPAP to a nasal cannula, allowing provision of additional oxygen if needed, at flows of less than 1 L/minute. Use of higher flows was shown by Locke et al. to generate unregulated positive end expiratory pressure, depending on the size of the cannula, flow rate, and size of the infant's nasal passage (Locke et al. 1993). Sreenan et al. used flows of up to 2.5 L/minute and provided a formula for adjusting cannula flow based on infant weight to generate a "safe" end expiratory pressure (Sreenan et al. 2001).

The ease of cannula use and the complications of nasal and facial trauma reported with NCPAP (Robertson et al. 1996, Fischer et al. 2010, Hogeling et al. 2012) have made use of the nasal cannula for respiratory support increasingly popular. Manufactured devices for heated and humidified "high-flow" nasal cannulae (HFNC) with capabilities of providing flows well above 1–2 L/minute appeared in the early 2000's. Two of these devices (Vapotherm, Stevensville, MD; and Fisher&Paykel Healthcare, Irvine, CA) were studied by Kubicka et al., who concluded that at high flow rates with the mouth closed, unpredictable NCPAP was generated and that the HFNC should not be used for the purpose of NCPAP provision (Kubicka et al. 2008).

A Cochrane review of HFNC from 2011 concluded that insufficient evidence was available concerning the safety and effectiveness of this therapy (Wilkinson et al. 2011). However, two large randomized trials were published shortly thereafter. In a multicenter randomized noninferiority trial, Manley et al. 2013 assigned 303 low

birth weight infants (mean birth weight about 1040 g, mean gestational age about 27.5 weeks) to HFNC (5–6 L/minute) or NCPAP (7 cmH₂O) after extubation. Treatment failure, defined by specified respiratory parameters, was 34.2 % in the HFNC group and 25.8 % in the NCPAP group. This difference fell within the authors' predefined noninferiority difference of 20 %. However, questions have arisen as to whether this margin was clinically justified (Nagar et al. 2013). Half the infants who failed HFNC were successfully treated with NCPAP. In the second study, Yoder et al. studied 432 infants of 28–42 weeks' gestation who were randomized to HFNC or NCPAP with prespecified flows and pressures. Infants could be randomized for primary therapy, or for treatment after extubation. There was no difference in failure, defined as intubation within the first 72 hours of study support (10.8 % HFNC; 8.2 % NCPAP). Infants on HFNC did remain on this study mode longer than infants on NCPAP ($p < 0.01$). No other differences between study groups were found (Yoder et al. 2013).

HFNC and NCPAP work by different mechanisms. While NCPAP provides pressure and improves the functional residual capacity (FRC), HFNC improves CO₂ elimination and washout of dead space. Correct application of a HFNC should limit the size of the cannula so that a large leak is present. Thus, though some distending pressure may result, the danger of high and uncontrolled pressure is minimized and the effectiveness of gas washout and entrainment of gas around the cannula can be maximized. For excellent review and description of these concepts see Dysart et al. and de Jongh et al. (Dysart et al. 2009, de Jongh et al. 2014). The heat and humidification provided by HFNC systems is also a significant advantage over non-heated low flow cannula systems (Greenspan et al. 1991).

For the extremely low birth weight infant (<1000 g or <27–28 weeks) in whom little data are currently available for HFNC use, or for any infant with significantly decreased FRC, use of NCPAP is likely a better choice. For other infants, HFNC appears to be an option, provided that correct cannula size is employed.

7.6 Conclusions and Future Directions

Clearly NCPAP is an important therapy for infants with many causes of respiratory distress. Review of the Summary Tables of evidence currently available indicates that NCPAP is advantageous when used early, especially with surfactant, and for successful extubation. Pneumothorax appears to be more common with NCPAP, especially if surfactant is not used in a timely fashion or close attention is not paid to delivered pressure. Sufficient studies have not yet been done to definitively recommend one device over another. Variable-flow NCPAP appears to decrease work of breathing and may be most useful in the smallest infants. Bubble NCPAP and bi-level NCPAP may improve gas exchange.

Importantly, practitioners should be aware of how NCPAP may help their patients as well as where evidence is lacking, know potential complications, differences among devices, and be always willing to revise their patient care practices in the face of new data.

Essentials to Remember

- NCPAP is an important pillar of respiratory support in the neonate. It can prevent complications of intubation and mechanical ventilation, decrease the need for these interventions, and prevent extubation failure.
- Early NCPAP with selective surfactant therapy decreases death or BPD compared to prophylactic surfactant.
- Various types of NCPAP are available and their differences must be understood to use each of them correctly and optimally.
- High-flow nasal cannula can be an alternative to NCPAP. Optimal use of both HFNC and NCPAP requires understanding the differences in how they affect gas exchange.

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Educational Goals

- Understand the differences between conventional and high-frequency ventilation.
- Comprehend constant- and variable-flow delivery systems.
- Appreciate the importance of monitoring.

8.1 Conventional Mechanical Ventilation

8.1.1 Classification of Mechanical Ventilators

Steven M. Donn and Sunil K. Sinha

8.1.1.1 Introduction

A mechanical ventilator is an automated device that provides all or part of the work of breathing for patients with impaired respiratory or neurologic function. In order to safely apply a mechanical ventilator to a patient for continuous use, four requisites must be met (Table 8.1). First, there must be a way to create a stable attachment of the device to the patient, referred to as the interface. Second, there must be an energy source to drive the device. Third, the size and timing of the inflation must be regulated or controlled. Fourth, there must be a system to adequately monitor the performance of the ventilator and the status of the patient. This should include adjustable alarms to alert the clinician to undesirable and potentially dangerous conditions Chatburn (2003).

8.1.1.2 Mechanical Ventilators

Mechanical ventilators can be broadly classified into two major categories based upon the size of the delivered inflation (Table 8.2). Conventional mechanical ventilators deliver tidal volumes, which are within the normal physiological range.

Table 8.1 Requisites for mechanical ventilators

1. Stable patient–ventilator interface
2. Energy source
3. Control and regulation of size and timing of inflation
4. Monitoring and alarm system

Table 8.2 Classification of mechanical ventilators

<i>Conventional mechanical ventilator (tidal)</i>
Negative-pressure ventilation
Positive-pressure ventilation
Continuous flow
Pressure limited
Variable flow
Pressure control
Pressure support
Constant flow
Volume targeted
Hybrids
<i>High-frequency ventilation (nontidal)</i>
Jet ventilation
Oscillatory ventilation
Flow interruptors or percussive ventilators such as the Bronchotron

This is referred to as tidal ventilation, and it comprises the majority of mechanical ventilatory devices. High-frequency ventilators deliver much smaller tidal volumes. (Bunnell 2006). Actual measurements show the VT during HFOV is often > 2 ml/kg in patients with significant lung disease (Zimová-Herknerová and Plavka 2006). These will be considered in more detail in a subsequent chapter.

Conventional mechanical ventilators may also be subdivided based upon the method by which gas flow is introduced into the airway and lung. A gradient may be established by the application of positive pressure, in which gas is delivered to the patient through a circuit. Conversely, the gradient can be achieved through the creation of negative pressure. The patient is placed inside an incubator or chamber and sealed from the neck

down. Pressure within the chamber is cyclically decreased (usually by a vacuum pump), forcing gas to enter the airway. Negative-pressure devices, such as the iron lung, were commonly used during the poliomyelitis epidemic of the 1950s but are seldom utilized today. Thus, the overwhelming majority of mechanical ventilation performed on pediatric populations is provided by conventional positive-pressure ventilators.

Positive-pressure ventilation is usually powered by an electrical or compressed gas source. Electricity may be used to run compressors, which in turn create the driving force for ventilation. Compressed gas may also come from separate sources, such as tanks or wall outlets, allowing the blending of air and oxygen (Chatburn 2003). Because compressed gas is devoid of humidity and is damaging to the respiratory epithelial tissues, a heated source of humidification is added to the ventilator circuit (Schulze 2006).

The control system is used to be sure that the patient receives the desired pattern of respiration. The clinician chooses the pressure (peak inflation pressure, PIP) or volume (tidal volume, V_T) to be delivered, the baseline pressure (positive end-expiratory pressure, PEEP), the mandatory rate of mechanical inflation, how long the breath lasts (inspiratory time, T_i), and how much effort the patient has to exert (assist sensitivity) to trigger the ventilator. If the breath is triggered by the patient, it is referred to as a spontaneous breath; if it is initiated by the ventilator, it is referred to as a mandatory or control breath. Ventilator modes refer to the pattern of how spontaneous and mandatory inflation are delivered to the patient (Chatburn 2003).

Monitoring systems consist of both alarms, which notify clinicians when set parameters have been breached, and data displays, which may be digital or graphic. Alarms may signal disconnection of the patient from the ventilator or the ventilator from its power source. Circuit control alarms may indicate electronic failures

or ventilator settings which may be incompatible with ventilator function. Output alarms may warn of pressure, volume, or flow that exceeds or cannot meet the preset limits. Graphic displays include waveforms (or scalars) for flow, volume, and pressure over time, and numerous pulmonary “loops,” such as pressure volume or flow volume. Digital displays exist for multiple parameters, including peak pressure, end-expiratory (or baseline) pressure, inspiratory time, rate, and tidal volume. Many devices are also capable of calculating physiological measurements, such as mean airway pressure and minute ventilation, or pulmonary mechanics measurements, such as dynamic compliance or resistance. Storage of data and displays of

trends over time may assist in the interpretation of data and management of the patient (Fig. 8.1).

8.1.1.3 Continuous-Flow Systems

The creation of a device that offered continuous flow in the ventilator circuit enabled the development of neonatal mechanical ventilation. Because the intrinsic respiratory rate of the newborn is high relative to an older child or adult, the baby required a source of fresh gas to breathe between mechanical inflation. This is referred to as bias flow, and the rate is set by the clinician. When the ventilator exhalation valve closes during inspiration, the bias flow is diverted to the patient and the lungs are actively

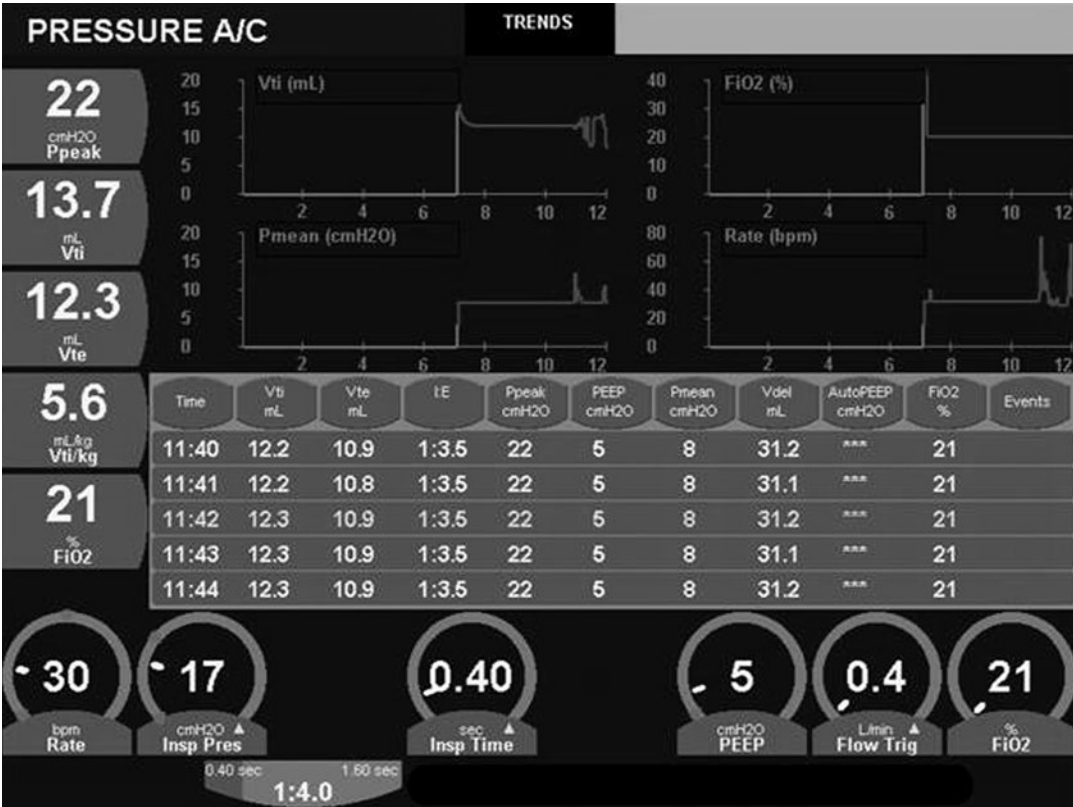
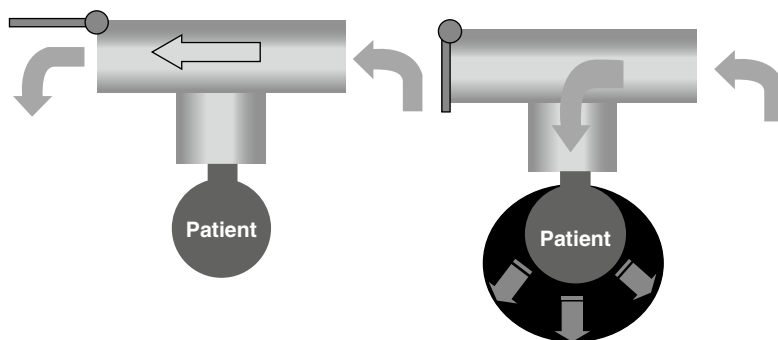


Fig. 8.1 Trend monitoring. Both graphic and analog data are trended here on a minute-to-minute basis

Fig. 8.2 Schematic drawing of continuous-flow, intermittent mandatory ventilation. On the *right side*, expiratory valve closes and gas flow is diverted to the baby, filling the lungs. On the *left side*, inspiration has ended, the exhalation valve has opened, and the lungs are passively deflating



inflated. At the end of inspiration, the valve opens, and the lungs are passively deflated by elastic recoil (Fig. 8.2).

The flow rate (in L/min) should be set high enough to allow the ventilator to reach the PIP in the allotted time. If it is set too low, the patient may develop air hunger and increased work of breathing. If it is set too high, it can create turbulence and ineffective gas exchange, lead to inadvertent PEEP, and result in overdistension of the lungs. Inappropriate circuit flow may result in rheotrauma (Donn and Sinha 2006), a component of ventilator-induced lung injury (Attar and Donn 2002).

Continuous flow is used during pressure-limited ventilation. This was the most common method of providing mechanical ventilation to neonates for more than a quarter of a century. Since the advent of microprocessor-based technology, two new ways to provide gas flow have been introduced into neonatal respiratory care.

8.1.1.4 Variable-Flow Systems

Variable-flow ventilation can be accomplished by actually controlling inspiratory flow through the use of proportional solenoid valves. This creates an inspiratory flow waveform that has a sharply accelerating phase followed by a rapidly decelerating phase (Fig. 8.3). This flow pattern is utilized in pressure-controlled ventilation and

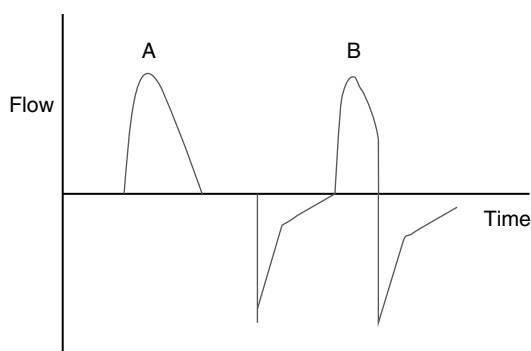


Fig. 8.3 Flow waveform, generated by measuring flow vs time. This is variable-flow ventilation, producing a rapidly accelerating then decelerating flow waveform. (A, B) On the left, breath is time cycled; on the left it is flow cycled

pressure-support ventilation. It results in rapid pressurization of the ventilator circuit and rapid delivery of gas to the lung, with peak pressure and peak volume delivery occurring early in inspiration. It may be thought of as a “front-end loaded” breath. Intuitively, this should be beneficial in pathophysiological states characterized by homogeneous lung disease where compliance is low and resistance is high (Donn and Boon 2009). Because flow is variable, some devices offer a qualitative way to control it through an adjustable rise-time feature. This alters the slope of the inspiratory pressure waveform. If the rise time is

too flat, air hunger may result. If it is too steep, pressure overshoot may occur. Careful adjustment helps to achieve the appropriate degree of hysteresis in the pressure–volume loop.

A major drawback of both continuous- and variable-flow ventilation is that although pressure is well controlled, volume will vary. At the same pressure, volume will be proportional to compliance. When the lung is stiff, tidal volumes will be low; when compliance improves, tidal volume will increase, and the clinician will need to make the appropriate adjustments.

8.1.1.5 Constant-Flow Systems

Constant-flow ventilation is utilized to provide volume-targeted or volume-controlled ventilation. Inspiratory flow accelerates at the start of inspiration but is held constant at the peak flow rate, creating a square flow waveform. This results in a ramping effect of both volume and pressure delivery, where both peak pressure and maximum volume delivery occur at the end of inspiration (Fig. 8.4). Thus, in contrast to pressure-targeted inflation, volume-targeted inflation are “back-end loaded.” They result in a slower inflation of the lung, and they may be more suitable to pathophysiological states characterized by nonhomogeneous lung disease, where rapid inflation would preferentially deliver more gas to the more compliant areas of the lung, creating or contributing to ventilation–perfusion mismatch.

True volume cycling (where inspiration ends after the delivery of a specific volume of gas to the patient) is not yet feasible in the neonate. Because endotracheal tubes are uncuffed, there is almost always some degree of leak around the endotracheal tube. In addition, the ventilator must be able to measure the volume of gas at the proximal airway, not at the machine. Some of the gas leaving the machine will be compressed in the ventilator circuit, especially when the lungs are stiff. This is referred to as compressible volume loss and can be substantial.

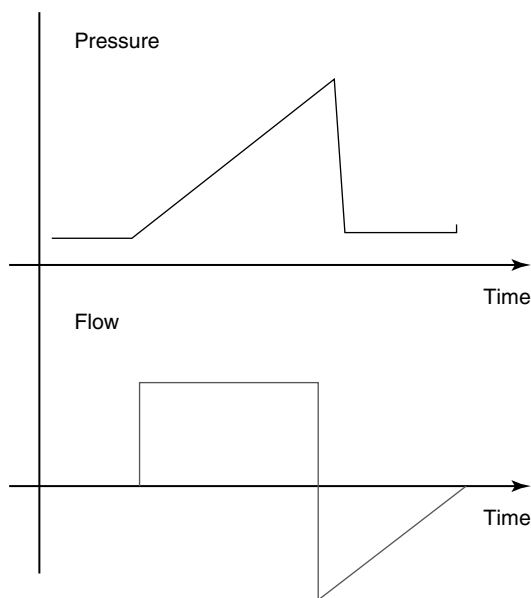


Fig. 8.4 Flow and pressure waveforms for constant-flow (volume-targeted) ventilation. Note the square configuration of the volume flow wave and the gradual increase (ramping) of pressure, creating a “shark’s fin” appearance

Constant-flow (volume-targeted) ventilation was briefly popular in the late 1970s, but technological limitations precluded its widespread use, and it was largely abandoned until the development of microprocessor-based ventilation and small, lightweight, low dead-space transducers. Recent clinical evidence suggests that this might be a better way to ventilate preterm infants with respiratory distress syndrome. One feature of constant-flow ventilation is the auto-weaning of pressure. As compliance improves, less pressure is required to deliver the desired tidal volume, and the machine adjusts the peak inspiratory pressure instantaneously. Theoretically, this should be advantageous in avoiding both barotrauma (by weaning pressure) and volutrauma (by limiting volume). Indeed, early meta-analysis of volume vs pressure trials has shown a decreased incidence of air leak, a decreased duration of mechanical

ventilation, and a strong trend toward decreased chronic lung disease. Recent trials are summarized in Table 8.3.

Conclusions

Neonatal mechanical ventilation has advanced dramatically over the past 10 years. The advent of microprocessor-based technology has revolutionized the concepts of ventilating newborns in respiratory failure. Strategies are now formulated based on the underlying pathophysiology and subsequently modified by the response of the patient and the interaction between the patient and the ventilator. Enhanced monitoring has improved patient safety. Long-term outcomes are still under investigation, but early information suggests that the future is indeed bright.

Essentials to Remember

- Conventional ventilation refers to systems that deliver gas volumes that approach physiological tidal volumes.
- High-frequency devices deliver gas volumes less than anatomical dead space.
- Constant-flow ventilation is used to provide volume-targeted ventilation.
- Variable-flow ventilation is used to provide pressure-controlled and pressure-support ventilation.
- Monitoring systems are critical to patient safety and ventilator performance.

8.1.2 Patient–Ventilator Interface

Steven M. Donn

8.1.2.1 Introduction

The interface refers to the way in which the ventilator circuit is connected to the patient. The interface is classified as *invasive* when the ventilator circuit attaches to a tube that is placed directly into the patient's hypopharynx (endotracheal tube) or trachea (tracheostomy tube) for the delivery of positive-pressure ventilation. *Noninvasive* ventilation refers to positive-pressure ventilation that

is delivered to the patient by a mask that covers the nose and mouth or by prongs or cannulas that are inserted into the nares. Systems that deliver negative-pressure ventilation may or may not use an interface with the airway (Chatburn 2003). This chapter will focus only upon invasive ventilation interfaces.

Educational Goals

- Understand the concepts of the patient–ventilator interface.
- Differentiate invasive and noninvasive ventilation.
- Comprehend the effects of the patient circuit and endotracheal tube on mechanical ventilation.

8.1.2.2 Effects of the Patient Circuit

The patient circuit consists of tubing which conducts gas flow from the ventilator to the patient (inspiratory limb) and from the patient to the atmosphere (expiratory limb). The inspiratory limb may also pass through a heated source of humidification.

The ventilator circuit has its own characteristics regarding compliance and resistance. This impacts the actual volume of gas which reaches the patient. If the circuit is very flexible and is easily distorted and the compliance is greater than that of the patient, less gas will reach the patient compared to a more rigid circuit. On the other hand, if the circuit is very rigid and the patient's lungs are very stiff, some of the gas within the circuit will be compressed and not reach the patient (Chatburn 2003). This is referred to as compressible volume loss and represents the difference between the volume of gas that leaves the ventilator and the volume of gas that actually reaches the patient airway.

Thus, the pressure, flow, and volume that actually reach the proximal airway are different from the settings that the clinician sets on the ventilator. A portion of this may result from errors in calibration or inaccuracy of measurement, but most relates to circuit compliance and resistance.

Table 8.3 Summary of key trials evaluating volume-targeted ventilation

Study	Randomization	Participants	Intervention	Outcome measures
Cheema and Ahluwalia, (2001)	Randomized double crossover trial	40 infants <34 weeks' gestation requiring mechanical ventilation for RDS Exclusions: Infants requiring muscle relaxants or with lethal congenital anomalies	SIPPV alone vs SIPPV + VG, or SIMV alone vs SIMV + VG	Primary: Peak airway pressure Secondary: Mean airway pressure, expired tidal volume, minute volume, FiO ₂ , and transcutaneous CO ₂ and O ₂ pressure
D'Angio et al. (2005)	Randomized controlled trial	213 infants who required mechanical ventilation and were at least 24 weeks' gestational age and weighed 500–1,249 g at birth	PRVC vs TCPL SIMV	Primary: Proportion of infants who were alive and extubated at 14 days of age Secondary: Proportion of infants who were alive and extubated at 28 days of age or 36 weeks post-conceptual age, age at final extubation, mortality, failure of ventilatory mode, incidence of BPD, air leaks, pulmonary hemorrhage, PDA, IVH, PVL, NEC, ROP, home oxygen use, and numerous other parameters
Herrera et al. (2002)	Randomized crossover trial	17 infants between 600 and 1,200 g with respiratory failure Exclusions: Severe congenital anomalies, perinatal asphyxia, sepsis, symptomatic PDA, Grade 3–4 IVH, sedation, and clinical instability as defined by attending neonatologist	First nine infants: SIMV alone vs SIMV + VG (4.5 mL/kg) Next eight infants: SIMV alone vs SIMV + VG (4.5 mL/kg) vs SIMV + VG (3 mL/kg)	Peak inspiratory pressure, mean airway pressure, number of ventilator and patient generated inflation, tidal volume, FiO ₂ , SPO ₂ , and TcPO ₂
Keszler and Abubakar, (2004)	Randomized controlled trial	18 infants <34 weeks' gestation with RDS on mechanical ventilation Exclusions: Patients with congenital anomalies, receiving neuromuscular paralysis or narcotic agents, or with >30 % endotracheal tube leak	Assist control only vs assist control + VG	Primary: Percentage of time that tidal volume and PaCO ₂ were outside target range (4–6 mL/kg and 35–45 Torr, respectively)

(continued)

Table 8.3 (continued)

Study	Randomization	Participants	Intervention	Outcome measures
Lista et al. (2004)	Randomized controlled trial Stratified by treatment center and gestational age (25–28 weeks and 29–32 weeks)	53 infants between 25 and 32 weeks' gestational age, on mechanical ventilation for severe RDS Exclusions: Lethal anomalies, use of paralytic agents, IVH (Grade 3–4), sepsis, or suspected infection	PSV alone vs PSV + VG (5 mL/kg)	Primary: Concentrations of IL-6, IL-8, and TNF- γ in tracheal aspirates on days of life 1, 3, and 7 Secondary: Duration of ventilation, airway pressure, incidence and rate of treatment for PDA, number of surfactant doses, incidence of air leaks, IVH, PVL, ROP, oxygen dependency at 28 days and/or 36 weeks post-conceptual age, and survival
McCallion and Morley (2005)	Meta-analysis of the following four trials: Keszler and Abubakar (2004) Lista et al. (2004) Piotrowski et al. (1997) Sinha et al. (1997)	178 infants <37 weeks' gestation Exclusions: Lethal congenital anomalies, muscle relaxation, suspected sepsis, lack of arterial access, narcotic use, ETT leaks >30 %, severe IVH, asphyxia, pneumothorax, and meconium aspiration syndrome	Volume-targeted vs pressure-limited ventilation	Primary: Hospital mortality Death or need for supplemental oxygen at either 28 days of life or 36 weeks' post-conceptual age Secondary: Failure of ventilatory mode or need for new use of muscle relaxants, duration of respiratory support, adverse blood gas measurements, PDA, air leaks, growth, IVH, PVL, neurodevelopmental outcome, need for supplemental oxygen at either 28 days of life or 36 weeks' post-conceptual age among survivors, and impact of mode of volume-targeted ventilation
Piotrowski et al. (1997)	Randomized controlled trial	60 infants with RDS or congenital pneumonia requiring mechanical ventilation and weighing <2,500 g Exclusions: Terminal state of infant at admission, air leaks, congenital anomalies, sepsis, and meconium aspiration	PRVC vs TCPL IMV	Primary: Duration of ventilation and incidence of BPD Secondary: Incidence of air leaks, IVH, hypotension, NEC, PDA, and need for sedation
Singh et al. (2006)	Randomized controlled trial A priori stratification into two groups according to birth weight (600–1,000 g and 1,001–1,500 g)	109 infants weighing between 600 and 1,500 g with gestational ages between 24 and 31 weeks, requiring mechanical ventilation and surfactant therapy Exclusions: Severe congenital malformations	VCV vs TCPLV Tidal volumes maintained between 4 and 6 mL/kg for both groups	Primary: Time from study entry until achievement of either an alveolar–arterial oxygen gradient <13 kPa (100 mmHg) or a mean airway pressure <8 cm H ₂ O for at least 12 h Secondary: Duration of ventilation or respiratory support, survival to discharge, incidence of CLD, IVH, PVL, PDA, or NEC

Singh et al. 2009	Long-term outcomes from prior RCT (Singh et al. 2006)	90 of the 109 infants in the 2006 study were followed Median corrected age at follow-up was 22 months	VCV vs TCPLV Patients prospectively followed with medical assessments and parental interviews via a structured questionnaire	Mortality, readmission rate, pulmonary outcomes (including the frequency of cough or wheeze and use of pulmonary medications), and gross neurodevelopmental outcome
Sinha et al. (1997)	Randomized controlled trial	50 preterm infants with RDS and birth weights of at least 1,200 g, requiring mechanical ventilation and surfactant therapy Exclusions: Pneumonia, sepsis, congenital malformations, lack of arterial access.	VCV vs TCPLV Tidal volumes maintained between 5 and 8 mL/kg for both groups	Primary: Time from study entry until achievement of either an alveolar–arterial oxygen gradient <13 kPa (100 mmHg) or a mean airway pressure <8 cm H ₂ O for at least 12 h Secondary: Incidence of IVH, PVL, PDA, or BPD at 36 weeks post-conceptual age

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SIPPV synchronized intermittent positive-pressure ventilation, *VG* volume guarantee, *PRVC* pressure-regulated volume control, *BPD* bronchopulmonary dysplasia, *PDA* patent ductus arteriosus, *IVH* intraventricular hemorrhage, *PVL* periventricular leukomalacia, *NEC* necrotizing enterocolitis, *ROP* retinopathy of prematurity, *SPO₂* pulse oximetry saturation, *TcPO₂* transcutaneous partial pressure of oxygen, *RDS* respiratory distress syndrome, *PaCO₂* partial pressure of arterial oxygen, *VCV* volume controlled ventilation, *TCPLV* time-cycled, pressure-limited ventilation, *CLD* chronic lung disease

Volume and flow leaving the ventilator is greater than that measured at the airway because of circuit compliance, whereas the pressure measured at the inspiratory side of the ventilator will be higher than that at the proximal airway because of circuit resistance (Chatburn 2003). Differences will also result from gas leaks anywhere in the circuit or connectors.

This is especially important during volume-targeted ventilation (see Sect. 8.1.3). Although the clinician orders a set volume of gas to be delivered to the patient, the actual volume reaching the proximal airway will be considerably less. For instance, even if a patient has reasonably compliant lungs and the circuit compliance is 0.5 mL/cm H₂O, less than half of the delivered gas volume will reach the patient. For this reason, it is imperative that measurements of tidal volume be performed at the airway and not calculated from the machine, especially in small, preterm babies, where even a small variance can have a huge impact (Cannon et al. 2000) (Fig. 8.5).

Because medical grade oxygen and air contain virtually no water, it is imperative that inspiratory gas be heated and fully humidified before delivery to the patient to avoid damage to the respiratory epithelium. Optimally, the temperature of the gas should be close to body temperature by the time it

reaches the airway (Schulze 2006). Condensation (rainout) in the ventilator circuit can be troublesome. It may disrupt laminar flow, causing turbulence and ineffective gas exchange. It may also be the source of auto-cycling in patient-triggered ventilation (see Sect. 8.1.3). Humidification will also affect the viscosity of the delivered gas and thus contribute to circuit resistance.

8.1.2.2.1 The Endotracheal Tube

During invasive ventilation, the ventilator circuit is ultimately attached to an endotracheal or tracheostomy tube. In neonatal intensive care, the most commonly used endotracheal tubes range from 2.5- to 4.0-mm internal diameter. They are inserted from 7 to 10 cm, measured from the lip (for orotracheal tubes), depending upon the size of the baby. It should be remembered that flow through a tube is proportional to the fourth power of the radius and is related linearly to the length. Choosing the proper tube size is important. If the tube is too small, resistance will increase substantially (Oca et al. 2002), the tube will be more prone to become obstructed, and there may be a significant leak around the uncuffed endotracheal tubes used in newborns and small infants. Leaks may interfere with proper functioning of the ventilator and result in significant discrepancies between inspiratory and expiratory tidal volumes.

Fig. 8.5 Preterm newborn infant receiving mechanical ventilation. Note the interface between the ventilator and the baby, consisting of ventilator circuit and its connection to the oral endotracheal tube



If the leak exceeds the trigger threshold, auto-cycling may occur (see Sect. 8.1.3). Conversely, if the endotracheal tube is too large, damage may occur to the anatomical structures of the airway. The depth of insertion is also important. If too high, inadvertent extubation may occur and gas leak may be more prominent. If too low, right main bronchus intubation may occur, with subsequent atelectasis of the left lung and overdistension of the right lung.

Clinicians must also be aware that despite adequate external fixation at the lip, the endotracheal tube is still mobile within the trachea, and the location of its tip changes with respect to changes in position of the head and neck. When the head is flexed, the endotracheal tube tip will move deeper into the airway; when the head and neck are extended or laterally rotated, the tip will be withdrawn (Donn and Kuhns 1980). Although it seems intuitive that better fixation can be accomplished with a nasotracheal intubation, this is not the case (Donn and Blane 1985).

Endotracheal tube position can be ascertained using a disposable capnometer to detect exhaled carbon dioxide, followed by radiographic confirmation. The capnometer is temporarily attached to the endotracheal tube connector and undergoes a color change from purple to yellow when exposed to carbon dioxide (Aziz et al. (1999). Because of the aforementioned tube movement, radiographs should be obtained with the patient's head and neck in a neutral position and in the midline (Donn and Kuhns 1980). Once verified in appropriate position, excess external length of the tube should be trimmed for the reasons cited in Table 8.4.

8.1.2.3 Apparatus Dead Space

Dead space classically refers to parts of the respiratory system that do not participate in gas exchange. Within the lung, gas exchange only occurs in the alveoli and terminal portions of the smallest airways. Gas exchange does not take place in the conducting airways, and this is often referred to as anatomical dead space. If, within the lung, there are areas of underperfused alveoli that are not participating in gas exchange, they are referred to as alveolar dead

Table 8.4 Complications of long external endotracheal tube length

Increased dead space
Increased resistance
Less efficient gas exchange
Increased work of breathing
Higher risk of kinking (obstruction)
Greater risk of inadvertent and self-extubation
Increased risk of infection (pooling of secretions)
More difficult to suction
Increased risk of auto-cycling

space. The anatomical and alveolar dead-space volumes are collectively referred to as total or physiological dead space. Wasted ventilation, the proportion of tidal gas that is delivered to the patient but not utilized in gas exchange, is defined by the ratio of dead-space volume to tidal volume (Chatburn 2003).

In this regard, the ventilator circuit and any attached apparatus can be thought of as an extension of the anatomical dead space, since not all of the gas flowing through it is involved in pulmonary gas exchange. This has also been referred to as mechanical dead space. Unless a way can be found to compensate for the increase in dead space, the imposed work of breathing will also increase.

Several devices, primarily used for monitoring, can now be added to the ventilator circuit but at the cost of additional dead space (Table 8.5). These include external transducers to measure flow, volume, or pressure; capnometers to measure end-tidal carbon dioxide; and stand-alone pulmonary function or mechanics devices, which are capable of measuring multiple parameters, including volumetric carbon dioxide (enabling the calculation of dead space to alveolar ventilation ratios). There are two types of capnometers: mainstream and sidestream. The mainstream capnometer may add considerable dead space, depending on the model, whereas sidestream capnometers do not. However, the risk of dilution by expired gas through entrainment of ambient air may adversely affect measurements (Sinha and Donn 2006a). Many centers prefer to use closed system suctioning devices, which are placed in line and add dead space to the circuit.

Table 8.5 Devices which add mechanical dead space

Flow, pressure, or volume transducers
Capnometers
Stand-alone pulmonary function or mechanics devices
Closed suctioning devices
Hygroscopic heat and moisture exchangers

Hygroscopic heat and moisture exchangers are sometimes used in place of a heated humidification system and can also add appreciable dead space (Schulze 2006).

8.1.2.4 Imposed Work of Breathing and Pressure-Support Ventilation

The imposed work of breathing refers to the amount of work needed to overcome the collective effects of the endotracheal tube, ventilator circuit, and demand valve, if a demand system is used (Sinha and Donn 2006a). It may be thought of as the “tax” a patient must pay for receiving mechanical ventilation. The age-old adage of “breathing through a straw” is a suitable analogy for the imposed work of breathing.

The imposed work of breathing becomes more significant the more a patient breathes spontaneously. Spontaneous inflation must be supported in some way to overcome the imposed work of breathing. During most forms of mandatory mechanical ventilation, spontaneous inflation are supported only by PEEP, and thus, it is not hard to understand why weaning the ventilator rate and shifting the burden of respiratory work to the patient often fails as a weaning technique (Sinha and Donn 2006b).

Pressure-support ventilation (PSV) was developed to assist spontaneous breathing by overcoming the imposed work of breathing. It is an inspiratory pressure assist applied to spontaneous inflation. It is patient triggered, flow cycled, and pressure limited (see Sect. 8.1.3). Thus, the patient controls its onset by triggering it, its duration of inspiration (by flow cycling), and its frequency. The clinician sets the pressure limit (and thus controls the degree to which the breath is supported) and an inspiratory time limit, which the patient may not exceed. It may

be used in conjunction with synchronized intermittent mandatory ventilation (SIMV) or alone, if the patient has reliable respiratory drive. If the pressure is set high enough to provide a full tidal volume breath, the level of support is described as PS_{max} ; if the level is just enough to overcome the imposed work of breathing, it is described as PS_{min} (Sinha and Donn 2006a). The best estimate of PS_{min} in the newborn is the pressure required to deliver a tidal volume of 3–4 mL/kg (Fig. 8.6).

Although PSV is relatively new to the neonatal intensive care unit, there are multiple studies which have examined its mechanisms and clinical role in weaning newborns from mechanical ventilation (Nicks et al. 1994; Osorio et al. 2005; Reyes et al. 2006, Sarkar and Donn 2007, Gupta et al. 2009).

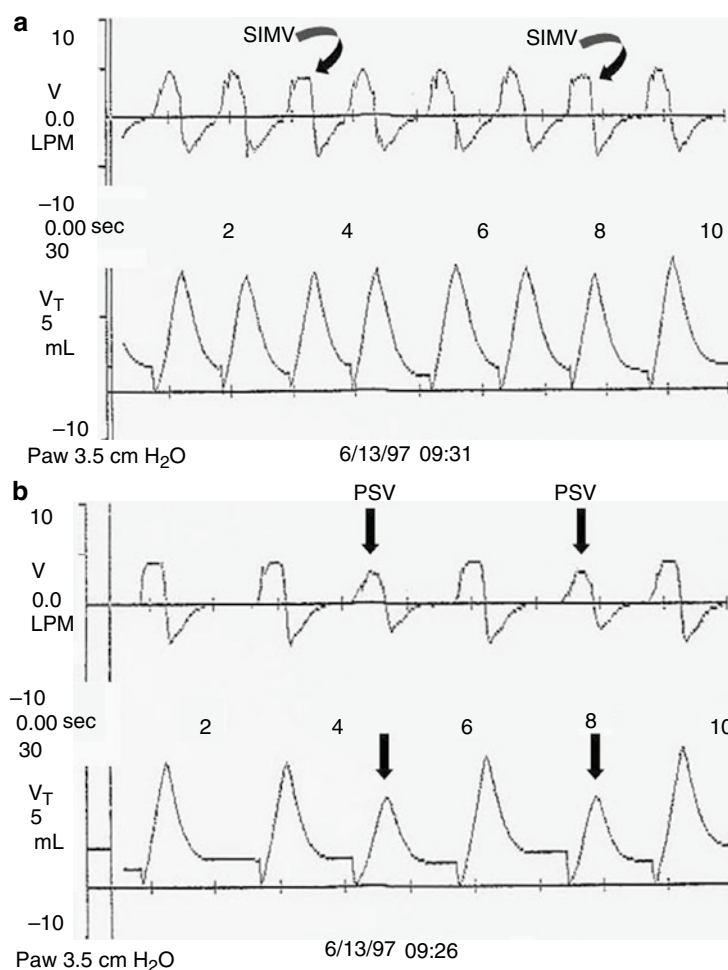
8.1.2.5 Summary

The patient–ventilator interface and ventilator circuit play important roles in determining the success of assisted mechanical ventilation. Careful attention must be paid to selecting the proper interface for invasive ventilation and to assuring its optimal location and fixation. The ventilator circuit and various devices, which can be added to it, such as capnometers and closed suctioning systems, also add mechanical dead space and increase the imposed work of breathing. Clinicians must find ways to compensate for this, by either adding more flow or volume or assisting spontaneous breathing by adding pressure support to spontaneous inflation.

Essentials to Remember

- The patient–ventilator interface and ventilator circuit are key elements of mechanical ventilation.
- Components added to the ventilator circuit add dead space and increase the imposed work of breathing.
- PSV is a novel way to help overcome the imposed work of breathing.

Fig. 8.6 Pressure support ventilation. Real-time pulmonary graphics showing flow and volume waveforms. **(a)** Patient is receiving PS_{max}. Note that the tidal volumes received during both the volume (square wave) SIMV inflation (arrows) and the pressure-support inflation are the same. **(b)** The patient is receiving pressure support to partially support spontaneous inflation (PSV). Note that the tidal volume delivery is less than that delivered during SIMV



8.1.3 Ventilator Modes

Steven M. Donn and Sunil K. Sinha

8.1.3.1 Introduction

Ventilator modes refer to the specific patterns of spontaneous and mandatory mechanical inflation. Spontaneous inflation are those initiated by the patient. They may or may not result in a mechanical breath, depending upon whether or not the patient is receiving triggered ventilation. Mandatory inflation are initiated by the ventilator based on an initiating factor, usually time.

Controlled ventilatory modes include intermittent mandatory ventilation (IMV), synchronized intermittent mandatory ventilation (SIMV),

and assist/control ventilation (A/C). In spontaneous ventilatory mode, pressure support ventilation (PSV) involves mechanical support applied only to spontaneous inflation, which may be combined with SIMV or used as a singular mode (Sinha and Donn 1996; Donn and Sinha 2001).

Educational Goals

- Understand the specific patterns of spontaneous and mandatory mechanical inflation.
- Recognize the three component waveforms: pressure, volume, and flow.
- Differentiate phase and control variables, and understand trigger variables.

8.1.3.2 Controlled Ventilation

8.1.3.2.1 Waveforms

The three airway signals, pressure, volume, and flow, may be plotted against time to produce graphic waveforms. An understanding of the waveforms is essential to comprehending how controlled ventilation works (Donn 1997; Sinha et al. 1996; Bhutani 2002).

The pressure waveform displays changes in airway pressure over time. If positive end-expiratory pressure is utilized, the baseline pressure will serve as the starting point for inspiration. As airway pressure increases during inspiration, the waveform will increase until it reaches its highest value, referred to as the peak inspiratory pressure (PIP). Pressure subsequently declines until it reaches the end-expiratory level. The area under the curve represents the mean airway pressure. Since oxygenation is a function of mean airway pressure, ventilatory maneuvers which increase the area under the curve may improve oxygenation. These include raising the PEEP, increasing the PIP, lengthening the inspiratory time, and to a lesser extent, increasing the rate.

The volume waveform looks similar to the pressure waveform, except that in the ideal situation, the waveform should reach the zero baseline at end expiration. Failure to do so indicates the presence of a volume leak around the endotracheal tube. The volume waveform peaks earlier in inspiration when pressure is controlled in contrast to the situation in which volume or flow is controlled, where the slope will be less.

The flow waveform differs from both the pressure and volume waveforms by having components that are both above the baseline (inspiration) and below the baseline (expiration). In other words, positive flow represents gas delivered into the airway, and negative flow represents gas egressing from the airway. As inspiration commences, there is a rapid flow of gas into the airway producing a sharp upswing in inspiratory flow, referred to as accelerating inspiratory flow. At its most positive level, this is referred to as peak inspiratory flow. Inspiratory flow then decelerates. However, note that this is still a positive value, thus airflow is still inspiratory although slower, and this component is referred to as decelerating inspira-

tory flow. Between the end of inspiration and the start of expiration, the flow waveform reaches a zero flow state (baseline) (An exception to this occurs during flow cycling discussed below). As expiration begins, there is an acceleration of expiratory flow, the sharp downward deflection below baseline, which at its most negative value is referred to as peak expiratory flow. Following this, expiratory flow decelerates, and although this scalar is in an upward direction, it is still negative and represents decelerating expiratory flow.

8.1.3.2.2 Control Variables

A control variable is the primary variable that the ventilator utilizes to produce the inspiratory phase of a mechanical breath. According to the equation of motion, there are three possible variables that can be controlled: pressure, volume, or flow. However, only one of these can be directly controlled at a time (Carlo et al. 2006; Chatburn 1995).

If pressure is the control variable, the pressure waveform will remain constant, even if there are changes in lung mechanics (compliance and resistance), and flow and volume will be variable. Positive-pressure ventilators control airway pressure, whereas negative pressure ventilators control body surface pressure.

If volume is the control variable, both the volume and flow waveforms will remain constant, and changes in lung mechanics will result in variability in airway pressure. True volume controllers must measure volume and use this measurement to control volume delivery. Volume may be controlled directly, using a device such as a piston or bellows, or indirectly by controlling airway flow (flow is defined as the time rate of volume delivery). Thus, true volume control is not technically possible in neonatal ventilation because cuffed endotracheal tubes are not used, and there is almost always some degree of volume leak around the endotracheal tube. For this reason, it is more appropriate to refer to this type of ventilation as volume-targeted or volume-limited (Sinha and Donn 2001).

If flow is the control variable, again both the volume and flow waveforms will remain constant, with pressure varying as lung mechanics change. The means for controlling flow include

simple flow meters or more technical proportional solenoid valves.

8.1.3.2.3 Phase Variables

Each breath, whether spontaneous or mechanical, consists of four phases: the initiation of inspiration, inspiration itself, the end of inspiration, and expiration. Phase variables refer to parameters that are measured and utilized to initiate, sustain, or terminate some phase of the ventilatory cycle. They consist of a trigger variable that initiates inspiration, a limit variable that restricts the magnitude of some parameter (i.e., pressure) during inspiration but which does not terminate inspiration, and a cycle variable that causes inspiration to end. Positive end-expiratory pressure is sometimes referred to as the baseline variable (Carlo et al. 2006).

8.1.3.2.3.1 Trigger Variables

A mechanical breath may start in response to a spontaneous breath (patient-triggered breath) or it may be initiated by the ventilator (mandatory or control breath). Patient-triggered inflation are initiated by a signal derived from the patient, which represents spontaneous respiratory activity, such as a change in airway pressure or flow. In the absence of a trigger mechanism, time is used as a trigger, where a mechanical breath is provided at intervals chosen by the clinician (Hird and Greenough 1991a; Hummler et al. 1996).

8.1.3.2.3.2 Limit Variables

Typically, limit variables restrict or maintain a parameter within the limits preset by the clinician. Pressure, flow, or volume can all be used as limit variables. An important distinction is that the limit variables are applied *during* inspiration but do not end it. It is a misnomer to consider time as a limit variable, because it actually *ends* inspiration and is thus a cycle variable.

8.1.3.2.3.3 Cycle Variables

When some variable reaches a preselected level, the inspiratory phase ends and the breath is *cycled* into expiration. The cycle variable refers to this measured variable used to end inspiration.

Time has been the most common cycle variable. The clinician chooses an inspiratory time

limit, and the inspiratory phase of the breath is terminated when this time elapses. Some devices allow the clinician to prolong inspiration through the use of an inspiratory hold. Inspiratory gas flow occurs during the inspiratory flow time, but during the inspiratory hold time, the exhalation valve remains closed, but there is no inspiratory gas flow. Here, the inspiratory time will be the sum of the inspiratory flow time and the inspiratory hold time. Time cycling is used as a “backup” mechanism during assist/control and pressure support ventilation, where flow is the primary cycle variable (see below). Phase variables refer to parameters that are measured and utilized to initiate or terminate some phase of the ventilatory cycle, e.g., cycling mechanisms.

Pressure cycling is used primarily for alarms. During pressure cycling, inspiratory flow is delivered until the preset pressure level is attained. Inspiratory flow then ceases and expiratory flow begins.

Volume cycling delivers inspiratory flow until a preset volume of gas has been delivered to the airway, after which inspiratory flow stops and expiratory flow begins. Some volume-cycled devices allow the clinician to maintain inspiration beyond this point by using an inspiratory hold, but in this case the cycle variable is time. An important distinction must be made between the volume of gas which leaves the ventilator and the actual volume that reaches the patient. These are not the same because of compression of gas within the ventilator circuit. Even if delivered volume is measured at the proximal airway, true volume cycling cannot be accomplished without a cuffed endotracheal tube because of gas leaks around an uncuffed tube (Sinha and Donn 2001; Hird and Greenough 1991a).

Flow cycling is a technique used to terminate inspiration when decelerating inspiratory flow has declined to a certain percentage of peak inspiratory flow. During flow cycling, inspiration cycles directly into expiration at this point, and there is only an instantaneous zero flow state between inspiration and expiration. Flow cycling allows the patient to control the duration of inspiration and thus improve patient-ventilator synchrony by adding expiratory synchrony, often called

an expiratory trigger (see below). Flow cycling also enhances patient safety. Because inspiration is terminated as a percentage of peak flow, the risks of inversion of the inspiratory-to-expiratory ratio ($I:E$), gas trapping, and inadvertent PEEP during patient-triggered ventilation (if the patient becomes tachypneic) are considerably less than with time cycling. During flow cycling, the actual inspiratory time will be less than the set inspiratory time when inflation is terminated by the flow change (Prinainak et al. 2003).

8.1.3.2.4 Controlled Modes of Ventilation

8.1.3.2.4.1 Intermittent Mandatory Ventilation

The original mode of mechanical ventilation was IMV. In this mode, the clinician chooses a set rate at which mechanical inflation will be delivered to the patient, and the ventilator will deliver the inflation at regular intervals. In between the mechanical inflation, the patient may breathe spontaneously. However, the spontaneous and mechanical inflation have no fixed relationship to one another and function independently. This may lead to asynchronous breathing and significant variability in delivered gas volumes. For instance, if the patient initiates a spontaneous breath while a mechanical breath is also in the inspiratory phase, the delivered gas volume will be considerably larger than in the situation where the patient is actively attempting to exhale against an incoming mechanical breath. This is frequently described as “fighting the ventilator.”

Asynchrony has been shown to produce numerous problems, including inefficient gas exchange, increased work of breathing, gas trapping and a higher incidence of thoracic air leaks (Greenough and Morley 1984), and irregular arterial blood pressure and cerebral blood flow velocity patterns. The latter have been associated with the development of intraventricular hemorrhage in preterm newborns with respiratory distress syndrome (Perlman et al. 1985).

Infants managed with IMV are frequently weaned from ventilatory support by reducing the IMV rate. This needs to be done cautiously. If done too rapidly, the baby may become

increasingly fatigued during the weaning process and may not tolerate extubation.

8.1.3.2.4.2 Synchronized Intermittent

Mandatory Ventilation

In SIMV, the clinician also sets a rate at which the mandatory inflation will be delivered, and the patient may also breathe spontaneously between the mandatory inflation. However, the ventilator attempts to synchronize the onset of the inspiratory phase of the mechanical breath to the onset of a spontaneous breath if one occurs within a timing window (Donn and Becker 2003). For example, if the SIMV rate is set at 30 inflation/min, a mandatory breath will be delivered approximately every 2 s. When it is time to deliver that breath, the ventilator will respond to the start of a spontaneous breath that occurs shortly before or shortly after that point. If no patient effort is detected within the timing window, a mechanical breath will be provided. Thus, SIMV removes much of the inspiratory asynchrony of IMV, but if the set inspiratory time is longer than the patient's own inspiratory time, expiratory asynchrony will still occur. This can be alleviated by using flow cycling.

As with IMV, spontaneous breathing between mandatory inflation is supported only by the baseline pressure (PEEP). Because babies have intrinsically high respiratory rates, both IMV and SIMV provide a higher work of breathing for the baby compared to A/C, because a large proportion of inflation are insufficiently supported. Use of either A/C or PSV (alone or in combination with SIMV) can overcome this problem. Problems similar to those for IMV also occur during weaning from SIMV.

8.1.3.2.4.3 Assist/Control Ventilation

During A/C, inflation initiated by the patient are “assisted” by the mechanical breath, while those that occur as mandatory inflation are “controlled.” Assist/control ventilation is accomplished by utilizing a trigger variable to respond to patient effort. In the newborn, this is most commonly derived from a change in airway flow (see below). If the spontaneous effort exceeds the

trigger threshold, the ventilator will respond by delivering a mechanical breath, which has a limit and cycling variable chosen by the clinician. If the patient fails to breathe or if the breath effort is insufficient to reach the trigger threshold, a control breath will be delivered at a rate set by the clinician. Thus, every patient breath that meets the trigger threshold will result in the delivery of a synchronized mechanical breath. The level of support during the assisted breath will be the same as during a control breath and is determined by the limit variables. For instance, inflation may be fully supported and deliver a full tidal volume or they may be partially supported (by adjusting pressure or volume) (Donn and Becker 2003; Greenough and Pool 1988).

Weaning during A/C is different from IMV or SIMV. As long as the patient is breathing above the control rate, further reductions in the rate will have no effect on the mechanical ventilatory rate (Sinha and Donn 2002). The primary weaning strategy during A/C is a reduction in pressure or volume. Some clinicians will extubate directly from A/C, while others prefer to switch to SIMV/PS during the weaning stage of illness.

Combining A/C with flow cycling can achieve complete synchrony between the baby and the ventilator. Inflation are initiated by spontaneous patient effort and they are likewise terminated in very close proximity to the end of the spontaneous inspiratory phase. Every breath is virtually identical, and numerous short-term physiological advantages have been demonstrated for A/C compared to either IMV or SIMV (Donn et al. 1994; Donn and Sinha 1998).

8.1.3.2.5 Synchronization Principles and Trigger Systems

8.1.3.2.5.1 Introduction

The concepts of patient-triggered and synchronized ventilation were practiced in adult and even pediatric respiratory care long before they became available to neonatal patients. Technological limitations precluded the ability to derive appropriate trigger signals and monitoring systems to safely accomplish synchronized ventilation until the decade of the 1990s.

As described above, one of the major problems with mechanical ventilation is asynchrony between the patient and the machine. Asynchrony results not only inefficient gas exchange but also contributes to respiratory and neurologic morbidity and increased cost of care. Until the advent of patient-triggered ventilation, clinicians had limited options to deal with asynchrony. Ventilator settings could be increased to try to “capture” or “overbreathe” the patient, but this was at the risk of increasing ventilator-induced lung injury. Patients could be sedated, but this often depressed the respiratory drive and prolonged the duration of mechanical ventilation. In severe cases, skeletal muscle relaxants could be used, but long-term administration resulted in numerous problems, including muscle atrophy, edema, and ventilator dependence.

8.1.3.2.5.2 Principles of Synchronization

Synchronized ventilation is an attempt to match spontaneous and mechanical breathing as closely as possible. It allows the patient to have control over some ventilator variables that were previously set by the clinician and which overrode the patient’s own breathing contributing to asynchrony.

The primary principle of synchronized ventilation is the use of a marker or surrogate of spontaneous breathing as a mechanism to trigger the delivery of a mechanical breath in as close proximity as possible to the spontaneous breath and to mimic the patient’s own pattern of breathing. Ideally, this should occur for both the onset of inspiration and the termination of inspiration. Thus, it should include both the trigger and cycle variables in its design (Greenough and Pool 1988).

There are additional concepts that are important to the performance of patient-triggered ventilation. First, the trigger signal needs to be a reliable indicator of spontaneous breathing and not an artifact resulting from movement of nonrespiratory musculature. Second, the trigger sensitivity has to be appropriate for the patient; if it is too difficult to achieve, the work of breathing will be higher, as spontaneous inflation will not be supported beyond the baseline pressure,

and if it is too sensitive, auto-cycling may occur (see below). Third, there needs to be a very short system response time or trigger delay. This time refers to the interval between reaching the trigger sensitivity and the rise in pressure at the proximal airway. If the trigger delay is too long, the patient may be nearly finished with the spontaneous inspiratory phase before help from the ventilator arrives. Finally, there should be minimal auto-cycling (false triggering) (Donn and Sinha 1998; Hird and Greenough 1990; Donn et al. 2000).

8.1.3.2.5.3 Trigger Systems

Various trigger systems were introduced into neonatal practice during the 1990s. As technological refinements occurred, several of these were replaced by systems with better sensitivity, shorter trigger delays, and less auto-cycling. In general, most systems now have trigger delays under 50 ms and work well on even the smallest patients (Laureen and Ronald 2000; Servant et al. 1992).

8.1.3.2.5.4 Abdominal Motion

One of the first trigger systems utilized in neonatal patients used a signal derived from abdominal motion during breathing (Hummler et al. 1996). An applanation transducer, such as the Graseby capsule, was placed on the abdomen and used to trigger a mechanical breath in response to spontaneous breathing. It appeared to work best in patients >2,000 g, but sensor placement was critical, and artifacts such as hiccups produced mechanical inflation unrelated to spontaneous breathing. In addition, there was only a single sensitivity setting, and tidal volume could not be measured. This technique has been largely abandoned.

8.1.3.2.5.5 Thoracic Impedance

Another early trigger system utilized changes in thoracic impedance, determined by standard electrodes used for electronic cardiorespiratory monitoring, to trigger inflation. In turn, the inspiratory cycle was terminated by active expiration. It, too, was dependent upon proper lead placement

and maintenance of contact gel beneath them. It was also unable to measure tidal volume (Ferguson 2006).

8.1.3.2.5.6 Airway Pressure

Changes in airway pressure are also utilized to trigger mechanical inflation. As the patient begins to breath, there is a slight reduction in airway pressure, which serves as the marker of a spontaneous breath. Proper setting of the sensitivity level is a key. Compared to flow-triggered systems, pressure triggering requires more patient effort and is less suitable for the smaller babies. This system is relatively easy to use and can provide data from numerous airway metrics (Hird and Greenough 1990; Laureen and Ronald 2000).

8.1.3.2.5.7 Airway Flow

The most popular method of providing neonatal patient-triggered ventilation involves the use of a signal derived from changes in airway flow (Laureen and Ronald 2000; Hird and Greenough 1991a). As the patient initiates a spontaneous breath, there is a slight acceleration of flow at the proximal airway. This can be detected by one of the two transduction methods. The first of these uses a pneumotachograph (a variable orifice, differential flow transducer). In the center of the transducer, there is a membrane, which is distorted proportional to the amount of flow. This signal is used to trigger the ventilator, and it can be integrated to provide volume measurements. The second of these uses a heated wire anemometer. As gas flows over it, it is cooled, and the amount of current needed to return the wire to baseline temperature can be converted to a flow and volume signal.

Flow transducers are extremely sensitive, detecting flow changes as small as 0.1–0.2 L/min. This is about the amount of flow necessary to propel a dust ball. They are ideally suited for the tiny patients in the neonatal intensive care unit. The downside of flow transducers is the higher tendency for auto-cycling described below.

8.1.3.2.5.8 Neural Triggering

Another means of triggering mechanical ventilation is the utilization of neural impulses. One such system uses a *neurally adjusted ventilatory assist technology in which a signal is derived when the vagus nerve stimulates the diaphragm*. The electrical activity of the diaphragm is captured, transmitted to the ventilator, and used to assist the patient's breathing. Both the ventilator and the diaphragm work with the same signal, minimizing trigger delay and theoretically reducing the risk of auto-cycling (see Sect. 8.1.3.3.4). There has been limited investigation of the technique in newborns, but it is an attractive hypothesis (Bernstein et al. 1995).

8.1.3.2.5.9 Auto-cycling

Auto-cycling is a phenomenon of patient-triggered ventilation. It occurs when something other than the patient's effort triggers the ventilator in a repetitive fashion, often producing a string of rapid, identical inflation on graphic monitoring.

Flow-triggered systems have the highest incidence of auto-cycling, most likely as a consequence of their extreme sensitivity. Auto-cycling most commonly occurs because of leaks, either in the ventilator circuit or around the endotracheal tube. If the leak exceeds the trigger threshold, the trigger system will interpret this as patient effort and provides a mechanical breath. If the leak persists, another breath is provided, and so on. Auto-cycling can also occur if there is excessive condensation in the ventilator circuit, as the oscillating water can create a flow change that exceeds the trigger sensitivity.

Clinicians must learn to recognize auto-cycling and distinguish it from simple tachypnea. The major graphic feature of auto-cycling is its regularity and similarity of all the inflation. Tachypnea usually shows some degree of breath-to-breath variability in both rate and configuration.

There are several ways to deal with auto-cycling. First, try to eliminate any source of leaks in the circuit or equipment and be sure that there is no condensation in the ventilator circuit. Second, if it appears that the leak is originating from the

airway, decreasing the trigger sensitivity may solve the problem. Some devices enable a measurement of the leak, and setting the sensitivity at a level that is slightly greater than this value can “fool” the ventilator and cease the auto-cycling (Donn and Becker 2003; Donn and Sinha 1998).

It is also important to realize that leaks may play havoc with flow cycling. If the leak is significant, the decline in the decelerating inspiratory flow waveform may not reach the termination point. This problem is eliminated by employing effective variable leak compensation in certain ventilators specifically designed for newborns with uncuffed ETT.

8.1.3.2.5.10 Clinical Evidence

Synchronized ventilation, whether provided by SIMV or A/C is clearly superior to IMV (Bernstein et al. 1994, 1996; Chan and Greenough 1994; Greenough et al. 2008). Virtually, every clinical trial has demonstrated short-term physiological benefit, including a shorter duration of ventilation, decreased thoracic air leaks, need for less sedation, and reduced hospital costs. Although there is a trend towards less chronic lung disease, it has been difficult to demonstrate this, as studies have been small and underpowered. It may also be affected by changing demographics, as smaller and more premature babies are now surviving. Nevertheless, IMV should be a mode of the past.

Essentials to Remember

- Modes of ventilation include IMV, SIMV, A/C, and PSV.
- The control variable is the primary variable utilized to produce the inspiratory phase of a mechanical breath.
- The phase variables refer to parameters that are measured and utilized to initiate, sustain, or terminate some phase of the ventilatory cycle.
- Synchronized ventilation is advantageous compared to IMV.

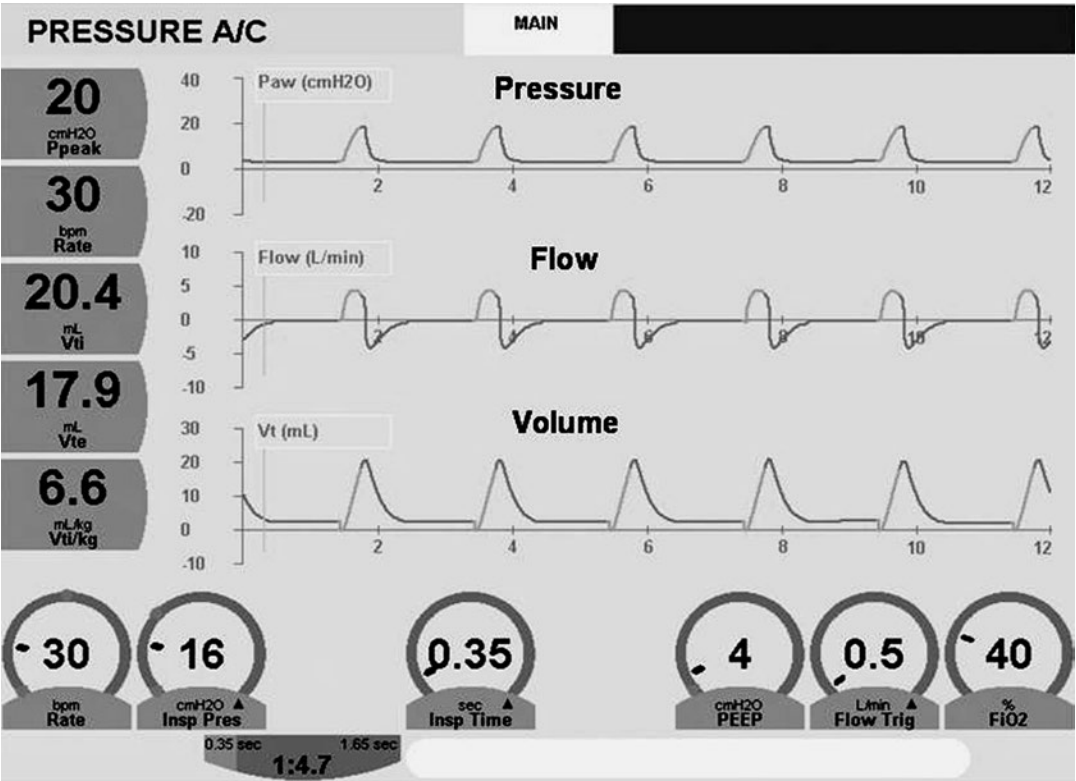


Fig. 8.7 Graphic waveforms. Pressure and volume (*top and bottom*) are similar and are always above the baseline. Flow waveform (*middle*) has two components. Inspiration is above the baseline and represents flow going into the patient (positive). This has accelerating (*upward*)

and decelerating (*downward*) phases. Expiration is below the baseline and represents flow coming from the patient (negative). It also has accelerating (*downward*) and decelerating (*upward*) phases

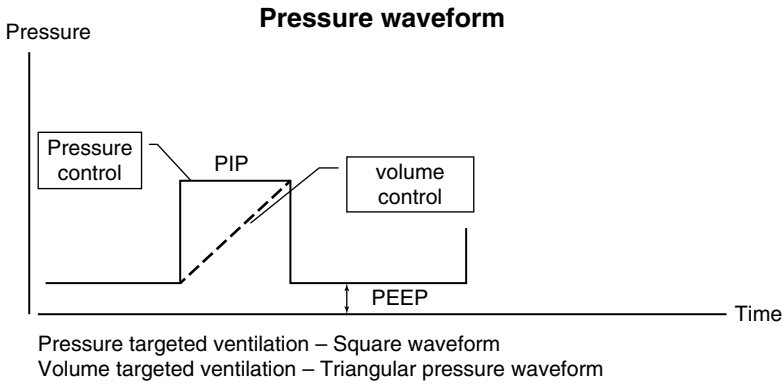


Fig. 8.8 Pressure waveform. Solid line represents pressure-targeted ventilation, which produces a square waveform. Dotted line represents volume-targeted ventilation, which produces a triangular or “shark’s fin” pressure waveform. Note that the expiratory portion of

the waveform is above the baseline representing positive end-expiratory pressure (*PEEP*). The area under the curve, bounded by the peak inspiratory pressure (*PIP*) and *PEEP*, is the mean airway pressure

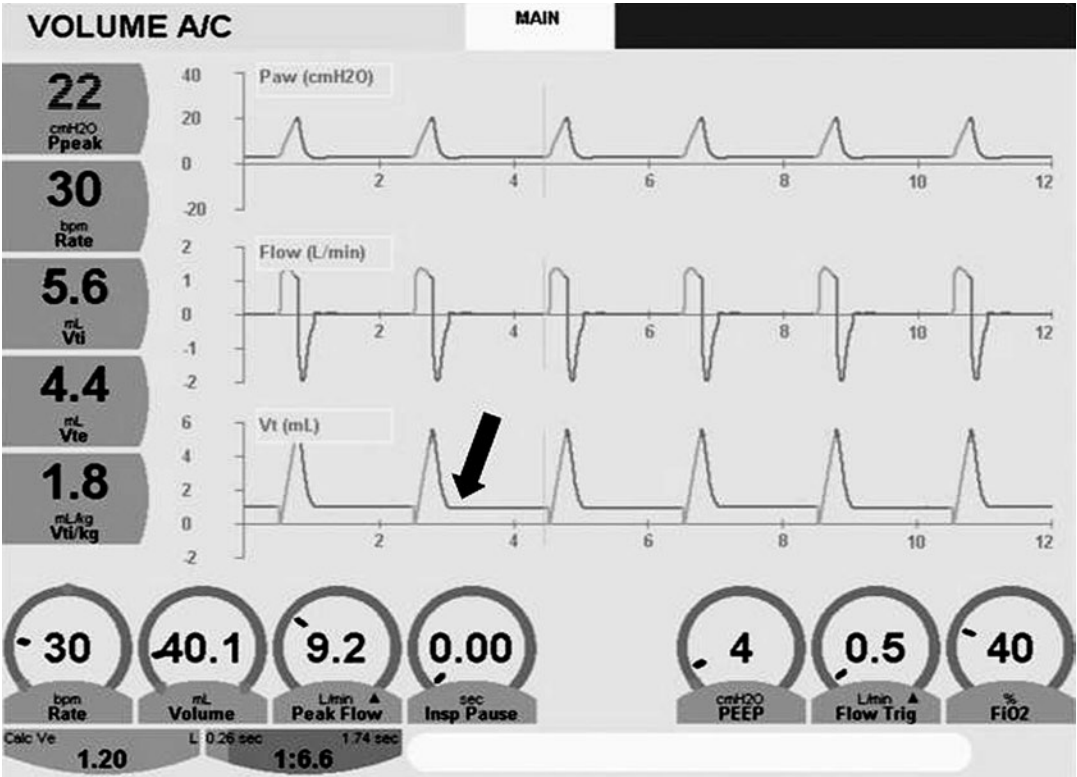


Fig. 8.9 The volume waveform fails to reach the baseline (arrow) because of a large endotracheal tube leak. Note discrepancy between the inspiratory (V_i) and expiratory (V_e) tidal volumes

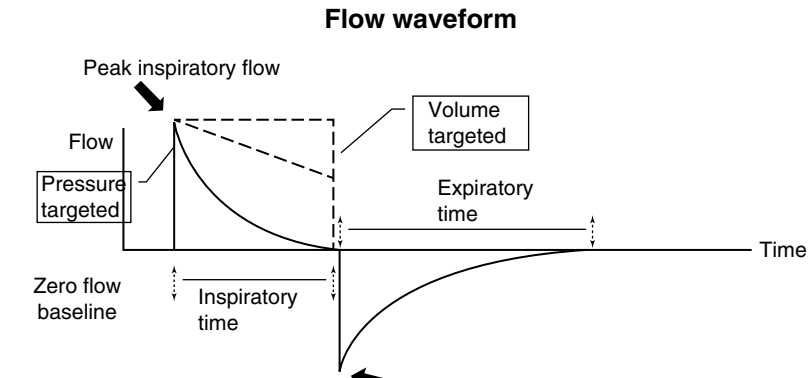
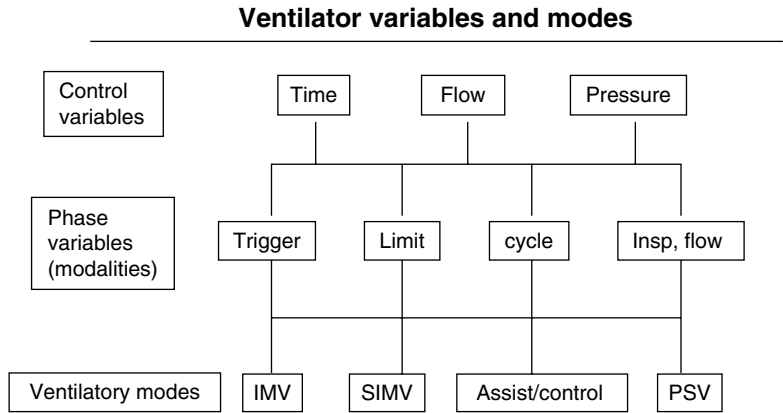


Fig. 8.10 Anatomy of the flow waveform. See text for description

Volume targeted ventilation – Constant square or deceleration flow
Pressure targeted ventilation – Variable decelerating flow

Fig. 8.11 Hierarchical classification of ventilator variables and modes. Although pressure support ventilation (PSV) is shown, it is a spontaneous and not a controlled mode



Phase variables

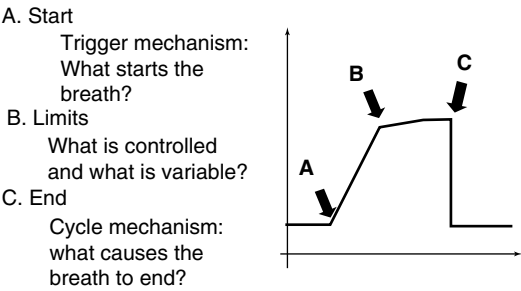


Fig. 8.12 Schematic diagram of a single ventilatory cycle noting points at which phase variables act

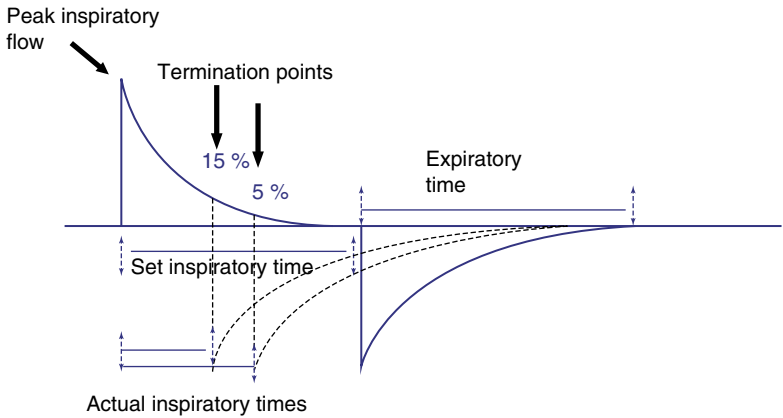


Fig. 8.13 Time versus flow cycling. When time is used to cycle a mechanical breath, inspiration ends when the pre-set limit has been reached. This may produce a prolonged zero flow state at the end of inspiration. When flow is used

to cycle the breath, inspiration ends at a preselected termination point as a percentage of peak inspiratory flow. The actual inspiratory time is less than the set inspiratory time and is controlled by the patient

Fig. 8.14 Graphic display of the differences between time and flow cycling. The first four inflation are time cycled. Note the prolonged zero flow state at the end of inspiration (time arrow), which produces a plateau of volume delivery. The last five inflation are flow cycled. Note how the decelerating inspiratory flow waveform transitions immediately into expiration at the termination point (flow arrow) producing a spiked volume delivery waveform

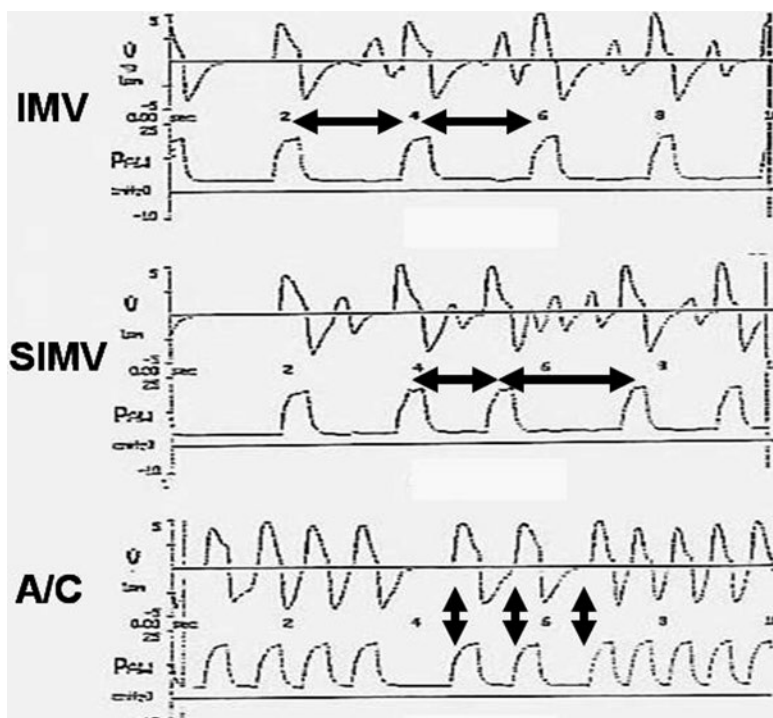
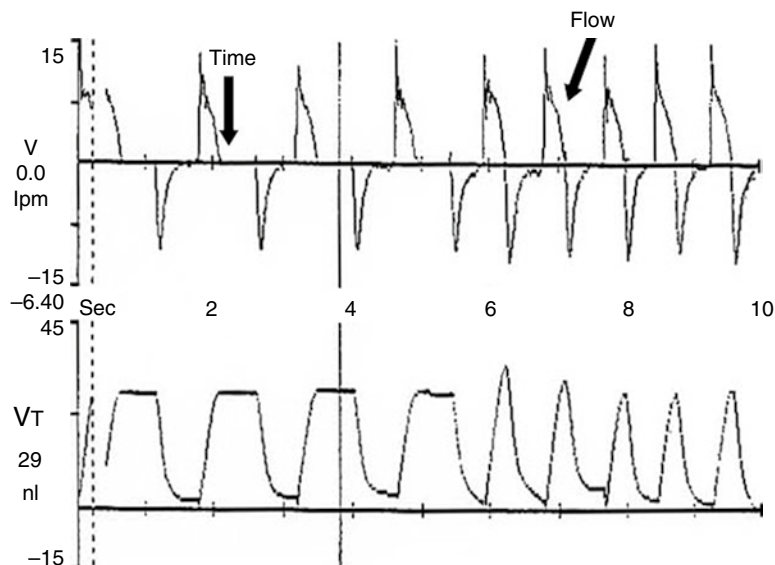


Fig. 8.15 Comparison of flow and pressure waveforms for intermittent mandatory ventilation (IMV), synchronized intermittent mandatory ventilation (SIMV), and assist/control ventilation (A/C). In IMV, mechanical inflation are delivered at regular intervals in accordance with the rate chosen by the clinician. Here, a breath is given every 2 s (note the intervals between the horizontal arrows), and the patient breathes spontaneously in between these inflation supported only by PEEP. In SIMV, the ventilator has a “timing window.” If the patient makes a detectable spontaneous effort, the ventilator will respond with a mechanical breath that is synchronized to the onset

of the spontaneous breath. If the patient fails to breathe, a mandatory breath is provided. Note how this produces an irregularity in the breath rate (differences in the horizontal arrows). Again, the patient may breathe between the mechanical inflation supported only by PEEP. In A/C, each spontaneous breath that meets the trigger sensitivity results in a synchronously delivered mechanical breath. If flow cycling is also used, complete patient–ventilator synchrony can be achieved. Note the complete relationship of the flow and volume waveforms (vertical arrows), whether the patient breathes at a slow or fast rate

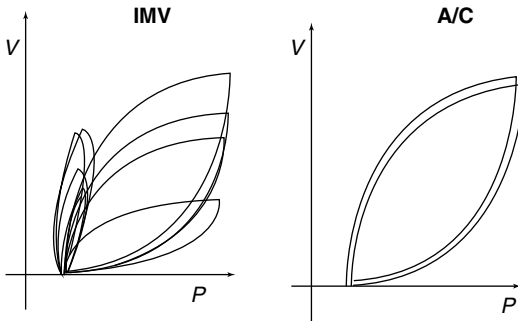


Fig. 8.16 Comparison of IMV and A/C. Note the variability in tidal volume delivery with IMV. Despite the fact that each breath reaches the same peak pressure, asynchrony results in wide differences in tidal volumes. During A/C, every breath is identical

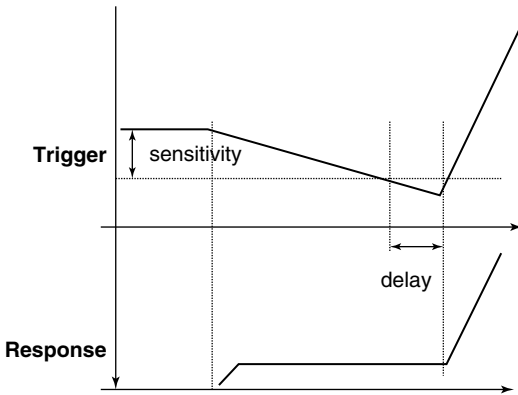


Fig. 8.17 Graphic representation of patient-triggered ventilation. The trigger responds when the patient meets the trigger sensitivity resulting in the delivery of a mechanical breath. The system response time, or trigger delay, is the interval between the trigger event and the rise in pressure at the proximal airway

8.1.3.3 Assisted Ventilation

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8.1.3.3.1 Pressure-Support Ventilation

Katherine C. Clement and Mark J. Heulitt

Education Aims

- Understand the characteristics of a pressure-support breath.

- Understand the three major phases of PSV.
- Understand the physiological effects on the breathing pattern, oxygenation and ventilation, and work of breathing.
- Understand the types of asynchrony during PSV and how it can be identified.

8.1.3.3.1.1 Introduction

Pressure-support ventilation (PSV) is a support mode used for spontaneously breathing patients. It augments inflation initiated by the patient which may improve patient-ventilator synchrony, reduce sedation needs, prevent disuse atrophy of respiratory muscles, and facilitate weaning (Brochard and Lellouche 2006; Sassoon et al. 2004). PSV may also improve work of breathing (Kornecki and Kavanagh 2007) and improve patient comfort (MacIntyre 1986; Thille et al. 2008).

8.1.3.3.1.2 Definition

PSV is a patient-triggered, pressure-limited, and flow-cycled form of mechanical ventilation used in patients with intact respiratory drive (Kornecki and Kavanagh 2007). A preset amount of positive pressure is delivered by the ventilator in synchrony with patient effort to raise airway pressure to a certain level (Brochard and Lellouche 2006). This preset pressure is known as the “pressure-support level” (Brochard and Lellouche 2006). A patient must generate a minimum negative inspiratory force that exceeds the preset ventilator flow or pressure sensitivity in order to trigger a breath from the ventilator (Kornecki and Kavanagh 2007). The set level of pressure support is then delivered and sustained until the ventilator senses the end of expiration, which is ideally a reflection of the end of patient demand (Brochard and Lellouche 2006). When inspiratory flow drops below a set threshold, which may be suggestive of relaxation of inspiratory muscles, the ventilator will cycle to the expiratory phase, open the expiratory valve, and release the pressure support (Brochard and Lellouche 2006).

With this mode of ventilation, patients are able to control their own rate, inspiratory time, and tidal volume (Kornecki and Kavanagh 2007). There are no mandatory inflation delivered; however, there is a safety feature on most modern ventilators in the case of apnea where the ventilator will automatically shift into a control mode (Brochard and Lellouche 2006).

The three major phases of PSV (initiation, pressurization, and cycling off) may vary among ventilators, may be altered by patient effort, and/or may be adjusted by the clinician in some circumstances. Patients must trigger the ventilator with their own active effort. Trigger sensitivity may be adjusted to improve a patient's ability to initiate a breath. Trigger delay is the time between the start of patient effort and the start of ventilator pressurization of the breath. Most ventilators respond in less than 100 ms, but there is some variability among ventilator models (Brochard and Lellouche 2006). The rate of pressurization also varies among ventilator models, but many allow for clinician adjustment. A regulatory mechanism should ensure the appropriate flow reaches the set pressure-support level and keeps the pressure constant until expiration occurs (Brochard and Lellouche 2006). A high speed of pressurization will produce a square pressure wave, whereas a lower speed of pressurization will attenuate this square shape (Iotta et al. 1991). Cycling off usually occurs when inspiratory flow falls below a specific threshold. This threshold can be changed on many ventilators (Brochard and Lellouche 2006). Sensing a small change in pressure above the set pressure-support level, which may represent patient expiratory effort, may be used alone or in combination with the flow threshold for cycling off. There is also typically a time limit set for the duration of inspiration (Brochard and Lellouche 2006).

8.1.3.3.1.3 Physiological Effects (Breathing Pattern, Ventilation/Oxygenation, Work of Breathing)

Because patients can control their own respiratory rate and partially control their own tidal volume, PSV would seem to provide a more

“physiologic” means of ventilatory assistance (Brochard and Lellouche 2006). However, the use of PSV actually changes the pattern of spontaneous breathing (Brochard et al. 1989; Ershowsky and Krieger 1987; Tokioka et al. 1989; Van de Graff et al. 1991; Hurst et al. 1989; MacIntyre 1987). Most patients will have an increase in tidal volume with a decrease in respiratory rate as the level of pressure support increases (MacIntyre 1986; Brochard et al. 1989; Ershowsky and Krieger 1987; Tokioka et al. 1989; Van de Graff et al. 1991). These findings suggest that breathing patterns rapidly change when respiratory muscles are faced with a new workload (Tobin et al. 1986) and imply that PSV can be adjusted according to the patient's breathing pattern response (Brochard and Lellouche 2006). Breathing patterns may change significantly with increasing PSV; however, minute ventilation may increase slightly or not change at all (Brochard et al. 1989; Ershowsky and Krieger 1987; Tokioka et al. 1989; Van de Graff et al. 1991; Hurst et al. 1989).

Gas exchange in PSV can be improved by enhancing alveolar ventilation, which results from an increased dead space to tidal volume ratio (Brochard and Lellouche 2006). PSV corrects PaCO₂ and respiratory acidosis for patients with hypercapnic respiratory failure (Brochard et al. 1989), and in healthy non-intubated patients, PSV of 10 cm H₂O decreases PaCO₂ significantly (Lofaso et al. 1992). Oxygenation is not significantly affected by changes in PSV compared to other modes of ventilation (Brochard and Lellouche 2006).

A major goal of PSV is to provide respiratory assistance while improving a patient's work of breathing. The decrease in work of breathing is significant and is proportional to the level of PSV (Brochard and Lellouche 2006). In one study, large swings in esophageal pressure generated only small tidal volumes, but when 20 cm H₂O of pressure support was added, small changes in esophageal pressure were related to larger tidal volumes (Brochard et al. 1989). These results support that the addition of PSV improves patient effort. The change in the pressure–volume ratio of the work of each breath decreases

progressively with increasing levels of pressure support in a lung model (MacIntyre 1986). Providing 5–10 cm H₂O of pressure support may reduce the work needed to overcome resistance in the ventilator circuitry and demand valve (Sassoon et al. 1991–1992). Individual patients have an upper limit of pressure support, above which work of breathing is worsened (Brochard and Lellouche 2006). Excessive pressure support can lead to asynchrony, apnea, desaturation, and ineffective efforts (Ershowsky and Krieger 1987).

8.1.3.3.1.4 Clinical Applications, Advantages, and Limitations

There are no exact guidelines for the clinical use of PSV (Brochard and Lellouche 2006). Adding PSV augments the pressure differences between the alveoli and the ventilator circuit, resulting in higher tidal volumes and inspiratory flow rates than spontaneous breathing alone (Brochard and Lellouche 2006). Often, the PSV is adjusted to achieve a tidal volume of 6–8 mL/kg (Brochard and Lellouche 2006). Assessment of accessory muscle activity and respiratory rate may assist in determining the ideal level of PSV (Brochard and Lellouche 2006; Brochard et al. 1989). Targeting a respiratory rate less than 32 inflation per minute (bpm) may be associated with decreased work of breathing (Brochard et al. 1989); however, a lower target rate (<25 bpm) may prolong weaning duration (Brochard and Lellouche 2006).

PSV is commonly used during weaning and assessment of extubation readiness, although evidence remains mixed. A low level of PSV can be used to simulate spontaneous breathing trials (Brochard and Lellouche 2006). PSV can also be used in combination with SIMV as a means for weaning, but there is not much data to support this (Brochard and Lellouche 2006). Using a low level of PSV has been shown to be equivalent or superior to T-piece trials in adults and infants (Esteban et al. 1997; Farias et al. 2001; Matic and Majeric-Kogler 2004).

Noninvasive ventilation (NIV) delivers gas through a face or nasal mask, providing ventilatory support without endotracheal intubation (Yañez et al. 2008). NIV is beneficial as an alternative to endotracheal intubation for adults with neuromuscular disorders, chronic obstructive pulmonary disease, respiratory distress, and cardiogenic pulmonary edema (Brochard and Lellouche 2006; Antonelli et al. 1998; Minuto et al. 2003). PSV is the usual mode of ventilation utilized with NIV. There is less data available for the use of NIV in children, but the initial studies are promising. In a retrospective series of 114 children with varying disease processes requiring NIV with PSV, Essouri et al. found a 77 % success rate in improving respiratory distress and avoiding endotracheal intubation (Essouri et al. 2005). Similarly, in a randomized, prospective study, Yanez et al. demonstrated improved oxygenation and respiratory effort in children with acute hypoxemic respiratory failure (Yañez et al. 2008). They also had a 47 % reduction in the rate of intubation (Yañez et al. 2008).

The advantages of PSV have been briefly mentioned earlier in this chapter. Patients are allowed to breathe in a more “physiologic” way since they control their own respiratory rate and partially control their own inspiratory time and tidal volume (Brochard and Lellouche 2006). This feature may provide improved patient–ventilator synchrony. In a comparison of SIMV and PSV, patients in PSV demonstrated improved subjective comfort, slower respiratory rates, and reduced muscle work (MacIntyre 1986). PSV also avoids disuse atrophy of respiratory muscles that can often result from controlled modes of ventilation (Sassoon et al. 2004). PSV does not have adverse effects on cardiovascular function in patients after cardiac surgery or with respiratory failure (Brochard and Lellouche 2006).

The primary disadvantage of PSV is that tidal volume is not guaranteed. Delivered tidal

volume depends, in part, on patient effort, which may continuously change with modifications in neurologic status (increased/decreased sedation), or altered respiratory mechanics (Kornecki and Kavanagh 2007). Oxygen demand and minute ventilation may also change over time, secondary to fever, stress, or pain, but preset pressure support remains constant (Kornecki and Kavanagh 2007). Additionally, if pressure support is high, a patient will decrease their respiratory rate and tidal volume and increase the risk of barotrauma. If pressure support is low, a patient will increase their respiratory rate and reduce their tidal volume, which will increase oxygen consumption and work of breathing (Marraro 2003). If there is inhomogeneous lung pathology, PSV favors ventilation of better aerated areas without affecting collapsed lung areas, potentially worsening ventilation–perfusion mismatch (Marraro 2003). PSV may not be highly recommended for pediatric or neonatal patients because the tidal volume cannot be controlled from breath to breath (Marraro 2003). Hypoventilation may alternate with hyperventilation. In small patients, maintaining appropriate tidal volume is critical for maintenance of alveolar ventilation and avoidance of ventilator-induced lung injury from volutrauma (Marraro 2003).

Volume support ventilation (VSV) is a volume-targeted form of PSV. Breath by breath, VSV adapts the inspiratory pressure support based on changes of the mechanical properties of the lung to ensure that the lowest possible pressure is used to deliver a preset tidal volume (Marraro 2003). As lung pathology improves, the ventilator automatically adjusts the amount of pressure needed to generate the set tidal volume, avoiding the risk of volutrauma associated with high preset pressures (Marraro 2003).

8.1.3.3.1.5 Asynchrony

Patient–ventilator synchrony is an ideal matching of patient demand with ventilator support.

Asynchrony is deleterious for patients because it may lead to increased need for sedation, increased work of breathing, respiratory muscle injury, ventilation–perfusion mismatch, dynamic hyperinflation, delayed weaning, increased length of hospital stay, and higher hospital costs (Nilsestuen and Hargett 2005). Asynchrony occurs in all modes of ventilation when a patient has spontaneous respiratory effort. PSV is thought to provide excellent synchrony with patient needs because it can identify both the beginning and end of a breathing effort (Brochard and Lellouche 2006). However, many types of asynchrony are still seen in PSV when the settings are not appropriate for patient demand. Three primary reasons for dyssynchrony in PSV are inappropriate pressure levels, inappropriate flow delivery, and inappropriate cycling-off criterion (Kacmarek and Chipman 2006).

The overall incidence of asynchrony during PSV in neonatal and pediatric patients is not well documented. In a recent animal study performed in young pigs recovering from lung injury, we found that when animals were healthy, the incidence of asynchrony occurred in 8 % of pneumatically triggered inflation (Heulitt 2012). When inflation were triggered via a neural signal from an EMG signal from the diaphragm, asynchrony was still low at 6 % of inflation. However, when the animal's lung was injured and after undergoing a recruitment procedure, the incidence of asynchrony in the pneumatically triggered inflation increased to 27 % of all inflation, while the neurally triggered inflation remained at 6 %. The level of asynchrony was directly related to increased response time and trigger delay in the pneumatically triggered inflation.

Inspiratory trigger delay is the time from when a patient starts their breath to when the inspiratory valve opens on the ventilator and the ventilator starts supporting the breath. Thus, it relates to the time from the beginning of inspiratory muscle activity to the beginning of mechanical inflation.

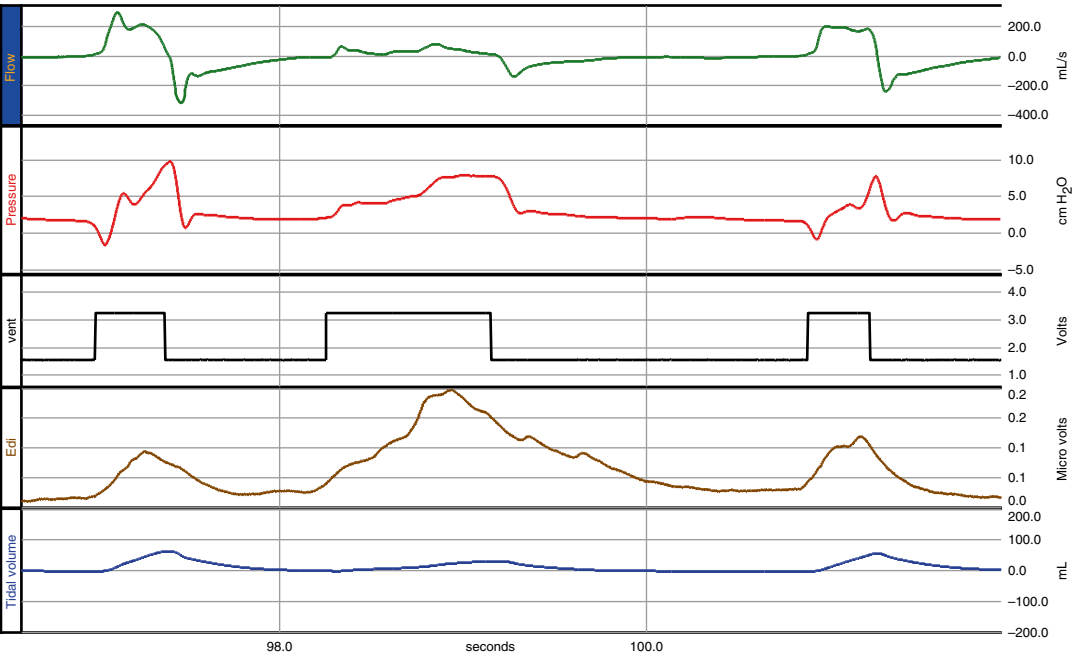


Fig. 8.18 Example of prolonged cycle due to trigger delay. Figure illustrates three inflation with waveforms of airway flow, pressure, and volume and ventilator trigger signal and diaphragm EMG tracing. In this example,

trigger delay caused the inspiratory time in the second breath to be greater than two times previous and subsequent inflation causing a prolonged cycle

This delay can lead to patient–ventilator asynchrony. Figure 8.18 is an example of trigger delay. In this example of recordings of flow, pressure ventilator trigger signal (duration of inspiratory valve opening), muscular response measured by EMG activity of the diaphragm, and volume asynchrony are demonstrated when the inspiratory time is twice the mean inspiratory inflation for other inflation during the same time sequence. As illustrated in this example, the second breath has a markedly prolonged inspiratory time as compared to the breath before and after.

Table 8.6 lists potential factors affecting duration of trigger delay. These causes relate to ventilator characteristics and settings, patient characteristics, and circuit characteristics and interfaces. Ventilator characteristics relate to the type and setting of the trigger. Flow-triggering systems require less patient effort (and thus have less trigger delay) than pressure-triggered systems (Brochard and Lellouche 2006). Triggering effort is 10–30 % of a patient’s total work of

Table 8.6 Factors affecting duration of trigger delay

Ventilator characteristics and setting	Type and setting of trigger
	Site of signal recording
	Ventilator valve design
	Level of pressure assistance
	Ventilator mode
Patient characteristics	Presence of dynamic hyperinflation
	Patient respiratory drive during trigger phase
	Upper airway resistance limited to noninvasive ventilation
Circuit characteristics and interfaces	Additional resistance (e.g., endotracheal tube, ventilator circuit, air sensor, HME)
	Presence of air leaks
	Accumulation of water in ventilator tubing

breathing, although the clinical implications of this are unclear (Brochard and Lellouche 2006). Inspiratory trigger delay can vary from 40 to 200 ms among different ventilator brands

(Richard et al. 2002; Aslanian et al. 1998). If a patient has intrinsic PEEP, he will have to expend even more effort for triggering (Aslanian et al. 1998).

Ineffective triggering is when a patient's inspiratory effort does not trigger a ventilator breath (Thille et al. 2006). This type of asynchrony is directly influenced by the level of PSV and the amount of dynamic hyperinflation (Brochard and Lellouche 2006). It is probably the most common form of asynchrony seen in patients on PSV. Excessive assistance will lead to hyperinflation of the lungs and will depress respiratory drive because of high tidal volumes and prolonged inspiration beyond the end of patient effort (Thille et al. 2006). If a patient is weak and/or the level of support is too high, he will be unable to decrease pressure or reverse expiratory flow enough to trigger the ventilator, and his effort will be wasted (Brochard and Lellouche 2006). Leung et al. found there were very few ineffective efforts below 60 % of assistance, but the number of ineffective efforts increased steadily as assistance increased (Leung et al. 1997). Respiratory cycles before these wasted efforts had higher tidal volumes and lower inspiratory times, both of which will lead to increased levels of hyperinflation (Leung et al. 1997). In a study by Thille, 85 % of asynchrony events were due to ineffective triggering (Thille et al. 2006). High pressure support levels and high tidal volumes were associated factors for ineffective triggering in these patients (Thille et al. 2006). In a second study, reducing the pressure support level completely eliminated ineffective triggering in 2/3 of patients and decreased tidal volume to 6 mL/kg predicted body weight (Thille et al. 2008). There was no increase in respiratory muscle energy expenditure and alveolar ventilation remained unchanged (Thille et al. 2008).

During auto-triggering, the ventilator is falsely triggered by a signal not related to a patient's inspiratory effort. This asynchrony is a type of trigger asynchrony and can be caused by leaks in the ventilator circuit, motion in the circuit, cardiac oscillations, or excessively sensi-

tive trigger sensitivity settings (Thille et al. 2006; Imanaka et al. 2000). A sudden increase in respiratory rate, a persistently high respiratory rate, or an absence of airway pressure drop at the start of an inspiration are all clues that the ventilator may be auto-triggering (Brochard and Lellouche 2006).

Two or more ventilator inflation delivered with a single patient effort are called multiple cycles or "double triggering" (Thille et al. 2006). Double triggering is also termed "stacked inflation" and is exemplified when the delta time between the ventilator trigger is less than one half the mean inspiratory time for inflation during time studied. Stacked inflation can occur with and/or without expiratory flow between the triggers. Figure 8.19 is an example of stacked inflation. Auto-triggering is one cause of this type of asynchrony as is a short ventilator refractory period (Brochard and Lellouche 2006). Double triggering often occurs when a patient's respiratory demand is high and the ventilator inspiratory time is too short (Tokioka et al. 2001). Tokioka et al. described multiple cycles during PSV when the cycling-off criteria were high (Tokioka et al. 2001).

The rate of the pressurization of a breath determines the initial upstroke of the pressure-time curve and is primarily dependent on the initial peak flow rate set on the ventilator (Brochard and Lellouche 2006). Flow dyssynchrony is related to the rise time, patient respiratory drive, and ventilator performance (Brochard and Lellouche 2006). Choosing a low rate of pressurization results in a greater length of time to reach goal levels of PSV and a convex initial airway pressure curve (Kacmarek and Chipman 2006). The longer it takes to reach the set pressure level, the greater the work of breathing for patients with both obstructive and restrictive lung disease (Bonmarchand et al. 1999). Figure 8.20 is an example of the convexity of the initial pressurization. In this example the presence of the convexity occurs after the inspiratory valve closes, and diaphragm muscular activity continues despite this closure. It is important to note that excessively fast pressurization, however, will lead to an initial overshoot beyond

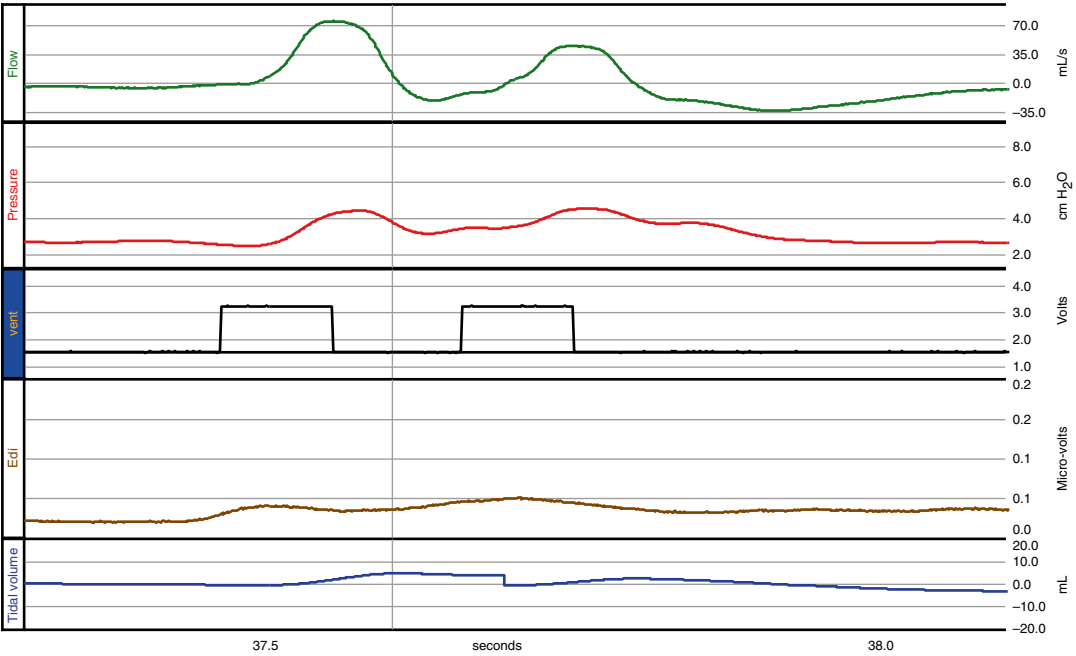


Fig. 8.19 Example of trigger asynchrony with stacked inflation. Figure illustrates two inflation with waveforms of airway flow, pressure, and volume and ventilator trigger signal and diaphragm EMG tracing. In this example delta

time between the ventilator triggers is one half of the mean inspiratory time for other inflation in the study. Stacked inflation occur with or without expiratory flow between the triggers

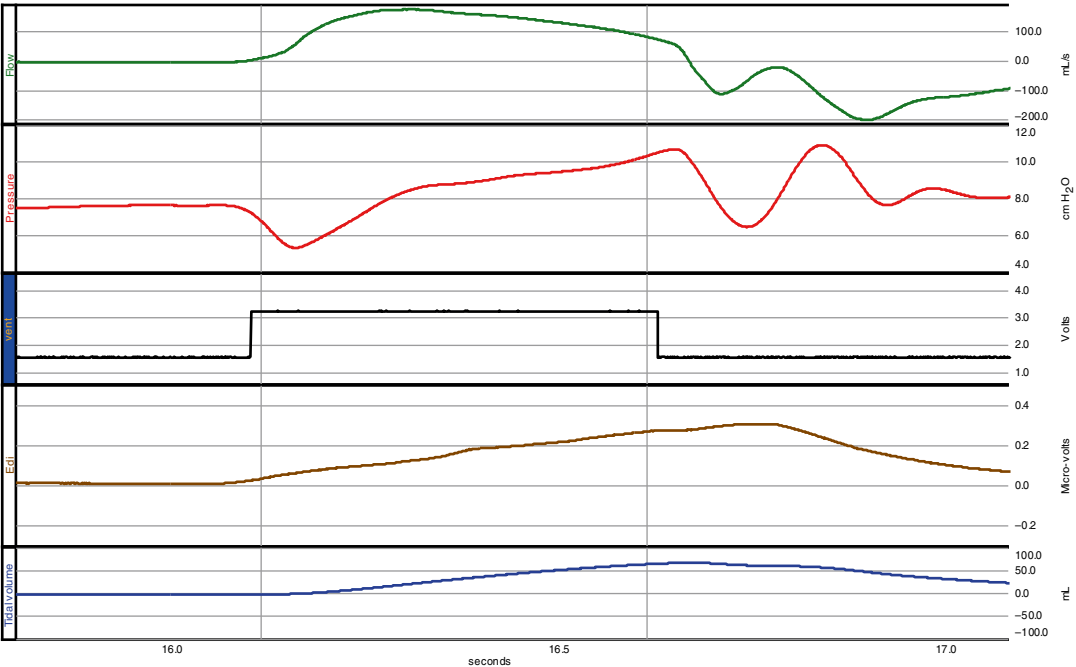


Fig. 8.20 Example of trigger asynchrony with effort without response. Figure illustrates two inflation with waveforms of airway flow, pressure, and volume and ventilator trigger signal and diaphragm EMG tracing.

In this example there is evidence of concavity of the pressure waveform. It is important to note that the muscular activity exemplified as the diaphragm activity occurs after the inspiratory valve closes

the goal pressure level, leading to potential early cycle termination related to high pressure and thus asynchrony (Brochard and Lellouche 2006).

If the cycling-off criterion is reached too early, the ventilator stops insufflation and opens the expiratory valve, while patient inspiratory effort continues (Brochard and Lellouche 2006). This type of asynchrony is referred to as early cycling off. It occurs when the cycling-off criterion is based on flow decay or time, as it is during PSV (Brochard and Lellouche 2006). If the expiratory valve opens while a patient is still actively inspiring, there is an initial drop in airway pressure and flow, followed by an increase, which results in a characteristic contour to the pressure–time curve (Tokioika et al. 2001). This type of asynchrony causes increased patient effort and prolonged neural inspiratory time (Brochard and Lellouche 2006).

Conversely patient characteristics such as dynamic hyperinflation may lead to delayed expiration which is the difference between the end of a patient's neural inspiratory time and the termination of inspiration by the ventilator (Brochard and Lellouche 2006). In PSV, the cycling-off criterion is typically a percentage of peak inspiratory flow rate, which often differs between patients with obstructive vs restrictive lung disease (Brochard and Lellouche 2006). Tokioika found an increase in tidal volume and decrease in respiratory rate when the cycling-off criterion was decreased from 45 to 1 %, and work of breathing was less with this low cycling-off criterion as well (Tokioika et al. 2001). This finding suggests that low cycling-off parameters should be considered in patients with acute lung injury (Brochard and Lellouche 2006). However, in patients with obstructive lung disease, a higher cycling-off criteria may be better (Tassaux et al. 2003). Low cycling-off criteria may cause insufflation to continue beyond patient neural inspiratory time, resulting in activation of a patient's expiratory muscles before the end of the ventilator breath, leading to short expiratory times and increased dynamic hyperinflation (Jubran et al. 1995).

For patients on noninvasive ventilation, prolonged inspiration can also occur, typically due to leaks around a mask (Calderini et al. 1999).

The cycling-off criterion can never be reached because of the leaks, and the ventilator continues to deliver a breath until the maximum inspiratory time (several seconds) is reached (Brochard and Lellouche 2006). Patients may then fight the ventilator in this situation (Brochard and Lellouche 2006).

Future Perspectives

Pressure support was introduced as mechanical ventilator mode in the 1980s. Since that time different technical advances have been introduced to allow patients to breathe spontaneously during PSV, for example, by the introduction of flow triggering. Currently patients breathing on PSV have a high incidence of asynchrony. Future advances have focused on redirecting the site of triggering from a generated at the patient's airway to one from an EMG signal from the patient's diaphragm. This signal theoretically has the advantage of decreasing trigger delay and allowing a closed-loop system to adjust the level of support to the strength of this signal.

Essentials to Remember

- PSV is a patient-triggered, pressure-limited, and flow-cycled form of mechanical ventilation used in patients with intact respiratory drive.
- The three major phases of PSV (initiation, pressurization, and cycling off) may vary among ventilators, may be altered by patient effort, and/or may be adjusted by the clinician in some circumstances.
- A major goal of PSV is to provide respiratory assistance while improving a patient's work of breathing. The decrease in work of breathing is significant and is proportional to the level of PSV.

8.1.3.3.2 Proportional Assist

Andreas Schulze and Eduardo Bancalari

Learning Objectives: To Understand

- The basic concept of proportional assist ventilation and respiratory mechanical unloading
- How the clinician can select ventilator settings with these modes that are specific for the individual type and extent of disease-related derangements in pulmonary mechanics (compliance, resistance, functional residual capacity)
- That volume-proportional assist (elastic unloading) is indicated in restrictive lung disease (low lung compliance)
- That flow-proportional assist (resistive unloading) is indicated in obstructive airway disease (high airway resistance)
- That PEEP influences the functional residual capacity during proportional assist as it does with other modalities
- Safety features during proportional assist ventilation such as backup ventilation modes and airway pressure limits

8.1.3.3.2.1 General Aspects

Patient-triggered ventilation typically synchronizes one or two events of the ventilator cycle to certain points in the spontaneous respiratory cycle. For example, the ventilator attempts to identify the onset of a spontaneous breath and subsequently delivers an upstroke in ventilator pressure. Other characteristics of the ventilator pressure contour such as peak inflation pressure and others remain preset by the clinician and may or may not match patient needs. The strategy of “proportional assist ventilation” (PAV) is fundamentally different from the conventional perception of a ventilator being a “pump” that is ignited by a trigger event. With PAV, the ventilator pressure steadily follows

a continuous input signal that is derived from the infant’s spontaneous breathing effort. This is achieved by an ongoing servo control of the ventilator pressure. The delivered pressure rises during inspiration in a fashion that is proportionate with a patient-derived signal at any point in time. During full-cycle “respiratory mechanical unloading” (RMU), the airway pressure is servo controlled throughout the entire respiratory cycle, not just during inspiration (Schulze and Schaller 1997). For such proportional amplification modes, the ventilator pressure has to track the input signal virtually without a time lag. This implies that near-perfect synchrony between the patient’s spontaneous effort and the ventilator can be achieved (Fig. 8.21). In addition, a relief in work of breathing ensues.

8.1.3.3.2.2 Clinical Application in Infants

When applying PAV/RMU, the clinician selects three *independent* settings to address *the individual degree* of impairment in compliance, resistance, and FRC:

1. The gain of elastic unloading (volume-proportional assist) which relieves elastic work of breathing for patients with “stiff lungs” (Schulze et al. 1993a). This gain is adjusted on a continuous scale in cm H₂O/mL (applied ventilator pressure per unit of tidal volume) (Fig. 8.22).
2. The gain of resistive unloading (flow-proportional assist) which relieves resistive work of breathing for patients with obstructive airway disease or those with a high-resistance endotracheal tube (Schulze et al. 1990). This is adjusted in cm H₂O/L/s (applied ventilator pressure per unit of airflow) (Fig. 8.23).
3. The PEEP which influences the FRC as it does during conventional mechanical ventilation (Schulze et al. 1993b).

A simple way to initiate PAV/RMU in a clinical setting is to start with zero gains so that the patient briefly breathes without the assist at constant positive airway pressure (CPAP). The elastic unloading gain is then gradually increased to a level judged as “appropriate” by clinical criteria such as reduction in chest wall

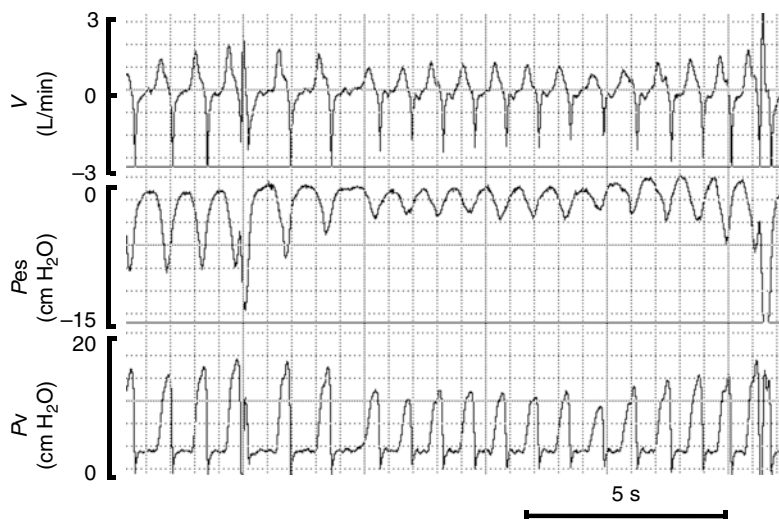
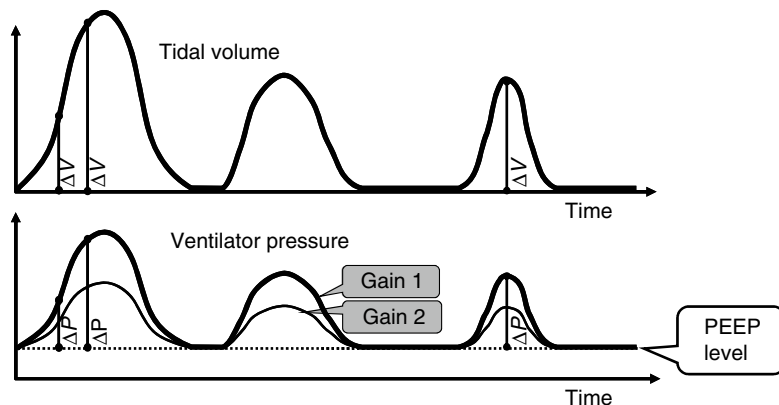


Fig. 8.21 Tracings for a preterm infant supported by proportional assist ventilation. Note the breath-by-breath variability in ventilator pressure which reflects the changing strength of the respiratory effort between inflation in this infant. Sighs (third and last breath on this recording) fail to induce major increases in ventilator pressure

because upper ventilator pressure limits are in place as safety feature. The ventilator pressure is aborted to the PEEP level when the upper pressure limit is reached, V' airflow as measured at the ventilator Y, P_{es} esophageal pressure, P_v ventilator pressure

Fig. 8.22 Schematic representation of spontaneous breathing during volume-proportional assist (elastic unloading) at two different settings (gain 1 and gain 2) of the assist gain level. Vertical lines demonstrate that the gain (ratio of change in ventilator pressure per unit of change in tidal volume) is maintained constant over time while the tidal breathing pattern varies. Gain setting two represents a lower level of the assist



$$\text{Gain} = \frac{\Delta \text{ Ventilator pressure } (P, \text{ cm H}_2\text{O})}{\Delta \text{ Tidal volume } (V, \text{ mL})}$$

distortion, physiological tidal volume, and regularity of breathing. It should be considered that smaller infants will need higher gains of elastic unloading (in absolute terms, i.e., in $\text{cm H}_2\text{O/mL}$) because tidal volume and compliance relate to body weight. As a general rule, infants below 1,000 g of body weight usually need about 1 $\text{cm H}_2\text{O/mL}$ or more of elastic unload-

ing gain while larger infants need less (Schulze and Bancalari 2001). The selected gain of resistive unloading should at least compensate for the resistance imposed by the endotracheal tube. This is about 20–30 $\text{cm H}_2\text{O/L/s}$ of resistive unloading for a 2.5-mm ID endotracheal tube. Higher gains may be required when pulmonary resistance is elevated.

Fig. 8.23 Schematic representation of spontaneous breathing during flow-proportional assist (full-cycle resistive unloading) at two different settings (gain 1 and gain 2) of the assist gain level. Vertical lines indicate that ventilator pressure changes occur virtually without a time lag to the airflow signal. The gain (ratio of change in ventilator pressure per unit of airflow) is maintained constant over time while the tidal breathing pattern varies. Gain 2 represents a lower level of the assist

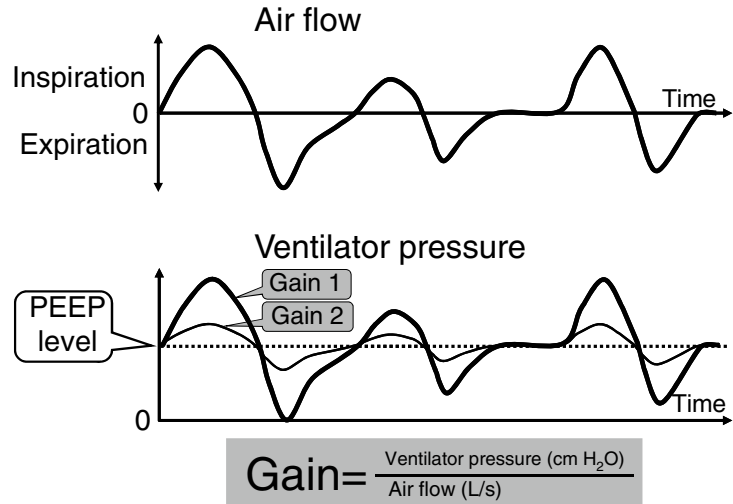
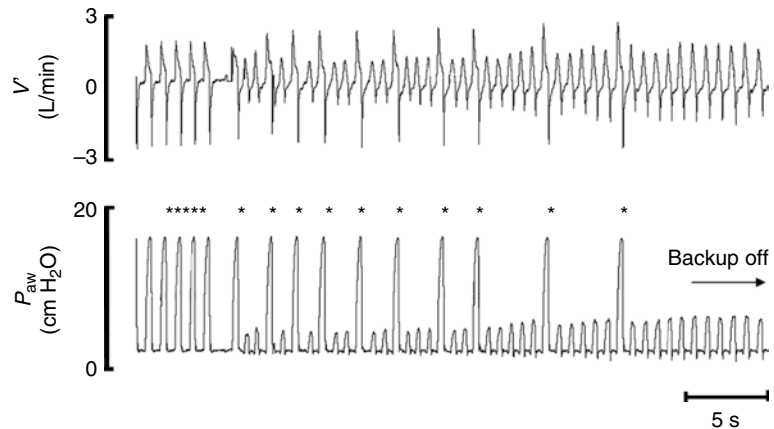


Fig. 8.24 Tracing of airflow (V), airway pressure (P_{aw}), and oxygen saturation (SpO_2) from an 840 g infant during backup ventilation and resumption of spontaneous breathing. Backup is gradually weaned by a stepwise reduction in the mechanical inflation rate until the full spontaneous breathing is recovered. Each spontaneous breath is supported by PAV. Asterisks indicate mechanical backup inflations



8.1.3.3.2.3 Backup Conventional Ventilation for Apnea and Hypoventilation

An automatic initiation of backup conventional ventilation is required not only during apneic episodes but also in the event of hypoventilation. Small inspiratory efforts will receive little ventilator pressure assist, and hypoventilation will occur if respiratory efforts decrease significantly. PAV modalities for infants should therefore include:

1. Initiation of backup ventilation in response to cessation of spontaneous breathing. The interval between the last detected breath and the onset of backup should be user adjustable because smaller and sicker infants tolerate less unsupported time.

2. Initiation of backup in response to a decrease in tidal volume below an adjustable threshold.
3. Gradual weaning from backup support when spontaneous breathing is resumed. This is necessary because breathing after an apnea is often initially weak and needs time to regain its former strength (Fig. 8.24). The ventilator should provide a feature which allows the user to adjust how fast backup is withdrawn (Herber-Jonat et al. 2006).

8.1.3.3.2.4 Technology

Spontaneous breathing activity drives the ventilator pressure output in the PAV/RMU modes by means of a feedback circuit. The driving signal can theoretically be obtained anywhere along the

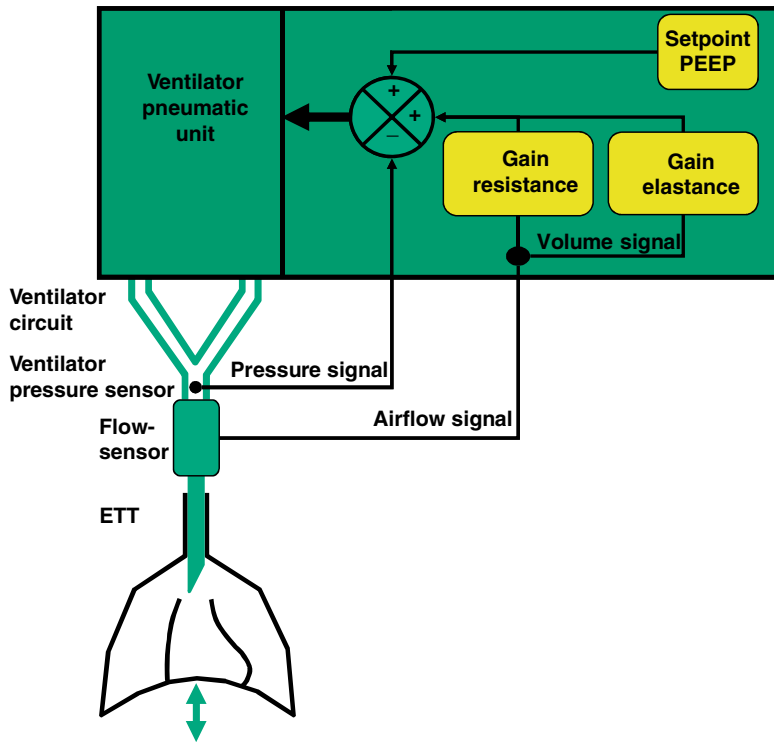


Fig. 8.25 Scheme of a ventilator system for PAV/RMU in infants. Airway pressure is sensed close to the endotracheal tube adapter and the signal is fed into a rapid negative feedback loop. To generate resistive unloading, i.e., flow-proportional assist, the airflow signal as measured at the endotracheal tube adapter is superimposed on the (negative) pressure-feedback circuit such that the airway pressure rises above CPAP during inspiration and decreases below CPAP when there is expiratory flow. To generate elastic unloading, i.e., volume-proportional assist, the tidal volume signal is obtained by integration of the airflow signal. After processing, it is superimposed on the pressure-

feedback circuit such that the airway pressure rises in proportion with the tidal volume. The user sets amplification factors (gains, K_R in $\text{cm H}_2\text{O/L/s}$ and K_E in $\text{cm H}_2\text{O/mL}$) for resistive and elastic unloading. The generated airway pressure is a servo-controlled, moving variable which is at any point in time a weighted sum of the airflow and tidal volume signal, added to the CPAP set point value $P_{aw} = (K_R \times \dot{V}) + (K_E \times V) + (\text{CPAP setpoint})$ (where $\dot{V}$ = airflow and V = volume). Because the system is software driven, almost every ventilatory modality can be generated provided that the hardware response times are sufficiently short

pathway from the respiratory center to the end organ, i.e., recorded as phrenic nerve activity, diaphragmatic electric activity, but also as tidal volume and airflow signals from probes inside the airway or from plethysmography. In this chapter, proportional amplification techniques will be explained that are based on tidal volume and airflow signals of spontaneous breathing. This is volume-proportional assist ventilation and flow-proportional assist ventilation, which is also called elastic and resistive unloading. Commonly, the driving signals are derived from flow probes mounted between the endotracheal

tube and the ventilator Y (Fig. 8.25). Ideally, ventilator pressure changes should occur in phase with the command signal derived from the airflow/volume signals. However, some mechanical delay is dictated by the system's inherent compliance, resistance, and inertance and will inevitably occur. PAV/RMU for preterm infants with their typical high respiratory rates and very small tidal volumes require exceptionally rapid feedback circuitry, low internal ventilator circuit compliance, and precise airflow/volume tracking.

Depending on the selected gains, the ventilator amplifies the output (which is the ventilation)

of the driving signal (which is the respiratory effort) more or less. Similar systems are widely used in electronic engineering. For example, a microphone–loudspeaker system works on the same principle: Sound waves are received, electronically transformed, their signal proportionally amplified, and used to drive the output of a sound wave generator. The gain, i.e., the degree of amplification, can be adjusted to suit individual circumstances.

8.1.3.3.2.5 Terminology and Therapeutic Objectives

While the basic concept of mechanical unloading for conditions characterized by impaired respiratory mechanics dates back to the 1950s (Biernson and Ward 1958), servo-controlled respiratory unloading devices with an appropriate dynamic response for adults (Poon and Huang 1987) and infants (Schaller and Schulze 1991) have been designed since the 1980s.

Investigators have used diverse terminology such as negative impedance ventilation, negative ventilator elastance and negative ventilator resistance, or resistive/elastic unloading (Schulze et al. 1993b). The term “proportional assist ventilation” as introduced in 1992 (Younes 1992) was meant to specifically denote a method of support in which the ventilator provides only *inspiratory* support in proportion to the instantaneous pressure generated by the respiratory muscles (P_{mus}), i.e., the simultaneous use of *both* flow- and volume-related assist with gains below the patient’s resistance and elastance.

However, all these devices share a common essential feature: They generate airway pressure in proportion to the instantaneous tidal airflow and/or volume with their respective proportionality factors (weights, gains) selectively adjustable by the user. Nevertheless, the different groups of investigators did have different specific objectives: Younes et al. primarily saw the technique as a means to amplify respiratory muscle effort (P_{mus}) and applied it in adults (Younes et al. 1992). Schulze et al. intended to use an infant ventilator to restore impaired lung mechanics to an “apparently” normal state. They therefore suggested to calculate the magnitudes of “negative

ventilator resistance and elastance” required to specifically compensate for the degree of an individual patient’s obstructive and/or restrictive lung disease. This concept of returning apparent respiratory mechanics back to normal also implied the use of unloading throughout the entire respiratory cycle (Schulze et al. 1990, 1993a).

8.1.3.3.2.6 Physiological Effects of PAV/RMU Effect on Elastance

“Elastance” (E) describes a behavior of a system in which a certain change in pressure occurs necessarily with a given change in volume. It can be measured in units of cm H₂O per mL. Lung elastance (E_l) causes a rise in lung elastic recoil pressure per unit of tidal volume gained. During a normal inspiration, a decreasing pleural pressure needs to be generated by the respiratory muscles to overcome the rising lung elastic recoil pressure. The inspiratory rise in elastic recoil pressure can be opposed by a rise in positive airway pressure. If the rise in positive airway pressure is applied by a ventilator such that it increases in proportion to the tidal volume, the ventilator itself exerts an “elastic behavior” characterized by the change in ventilator pressure per unit of tidal volume. This elastance of the ventilator (E_v) is equally quantifiable in cm H₂O/mL. However, while lung elastic recoil pressure tends to collapse the lung, the ventilator pressure acts in the opposite direction in the elastic unloading mode. Relative to lung elastance, the elastic “behavior” of the ventilator is therefore “negative.” When a patient is connected to a ventilator in the elastic unloading mode, the overall elastance of the combined system of lung and ventilator is equal to the arithmetic sum of the two elastic elements (because they are interconnected “in series”):

$$E_c = E_l + E_v$$

with E_v being a negative term.

The respiratory muscles work against this overall elastance of the combined system which becomes lower than lung elastance itself when the negative elastic behavior of the ventilator is added. If ventilator elastance is adjusted such that the overall elastance approaches the magnitude

of a normal lung's elastance, respiratory muscles will work on a system of apparently normal elastance. It follows that the patient's elastic work of breathing will then be in the normal range while the disease-related part of the elastic work of breathing is eliminated by the ventilator. To calculate the magnitude of ventilator elastance needed to achieve a "normal" overall elastance, the equation has to be solved for E_v :

$$E_v = E_c + E_l$$

For example, an infant weighs 750 g and has a measured respiratory system compliance of 0.3 mL/cm H₂O. The following steps are required to calculate precisely the gain of elastic unloading that returns the infant's elastic work of breathing to normal:

1. It is assumed that a normal lung of a newborn infant has a compliance of 2 mL/cm H₂O/kg. In a 750-g infant, a "normal" lung should therefore have a compliance of 1.5 mL/cm H₂O. Because *elastance* is the inverse of *compliance*, the target overall system elastance ("normal" lung elastance) should be $E_c = 1/1.5 = 0.67$ cm H₂O/mL.
2. Because the infant's measured lung compliance was 0.3 mL/cm H₂O, the elastance was $E_l = 1/0.3 = 3.33$ cm H₂O/mL, the applied ventilator elastance should be

$$E_v = 0.67 - 3.33 = -2.66 \text{ cm H}_2\text{O} / \text{mL}$$

Thus, if the ventilator is set to raise the airway pressure by 2.66 cm H₂O for each mL of tidal volume, this infant's elastic work of breathing would be in the "normal range."

This example shows that the required level of elastic unloading (gain) in cm H₂O/mL depends not only on the absolute stiffness of the lungs but also on body weight. Smaller infants will require higher gains. This is because "normal" lung compliance varies directly with body weight. Because the normal tidal volume in infants also varies directly with body weight, the respiratory muscle pressure amplitude required to generate a normal tidal volume is relatively constant across different body weights.

For clinical purposes, it is sufficient to base the estimate of the required elastic unloading

gain on measurements of *total respiratory system compliance* rather than *lung compliance*. The former variable is easier to measure because it does not require esophageal pressure manometry. Total respiratory system compliance is not very different from lung compliance in premature infants because of their soft chest wall (high chest wall compliance).

Effect on Resistance

Similar to elastic unloading, the applied ventilator pressure waveform during resistive unloading is in close relation to the *airflow* of spontaneous breathing, and this "behavior" can be described as a "negative resistance," i.e., a certain change in applied pressure per unit of airflow (cm H₂O of ventilator pressure per L/s). For a patient on a ventilator, the overall resistive load on respiratory muscles is the sum of the different components:

$$R_c = R_{aw} + R_{ETT} + R_v$$

with R_{aw} being the airway resistance, R_{ETT} the endotracheal tube's resistance, and the ventilator's resistance R_v , the latter being a negative term.

For example, an infant is intubated with a 2.5-mm inner diameter endotracheal tube. This endotracheal tube has an estimated resistance of 20 cm H₂O/L/s. If the gain of resistive unloading is set at -20 cm H₂O/L/s, the infant can breathe as if the endotracheal tube's resistance would not be in place. The ventilator specifically relieves the amount of additional resistive work of breathing associated with this endotracheal tube.

Effect on Chest Wall Distortion

Impairment of respiratory mechanics in infants is associated with increased chest wall distortion (CWD). CWD further increases respiratory muscles' work of breathing because work is "wasted" in distorting the chest. This reduces the efficiency of the respiratory muscles' to generate ventilation. Compensating for impaired respiratory mechanics by unloading decreases CWD and therefore improves the efficiency of respiratory muscles. This has been demonstrated in small adult and newborn animals who were intubated and had their lungs injured with

meconium (Schulze et al. 1998b) and in very low-birth-weight infants with acute respiratory illness (Musante et al. 2001). These studies have also shown that compared to unassisted breathing, a larger fraction of the tidal volume enters the chest compartment while the displacement of the abdominal compartment does not change much with respiratory mechanical unloading. Unloading can therefore provide a “stenting pressure” and stabilize the preterm infant’s highly flexible chest wall during spontaneous breathing.

Effects on Control of Breathing

Respiratory center output is increased in lung disease with impaired respiratory mechanics. It has been shown in animal models with severe pulmonary parenchymal failure that PAV/RMU decreases phrenic nerve activity while tidal volume rises and blood gases improve (Schulze et al. 1999b).

Overcompensation of Lung Elastic Recoil and Pulmonary Resistance

Magnitudes of unloading that equal or surpass lung elastic recoil (or pulmonary resistance) may induce a runaway of the ventilator pressure. In such situation, a small initial change in volume (airflow) triggers an increase in ventilator pressure higher than the accompanying rise in lung elastic recoil (flow-resistant airway pressure gradient) which in turn further increases lung volume (airflow). This positive feedback self-perpetuates because the negative elastance of the ventilator exceeds the positive elastance of the respiratory system. With such excessive gain settings, artifacts on the volume/airflow signal may initiate ventilator pressure runaway up to the set ventilator pressure limit or a set tidal volume limit. Unless ventilator pressure limits are in place, overcompensation of lung elastic recoil (excessive gains of volume-proportional assist) will lead to a self-perpetuating passive inflation. This process will not be terminated until overinflation leads to stiffening of the lung (increased lung elastance, decreased lung compliance) so that the ventilator pressure finally equals lung elastic recoil pressure (lung elastance equals the magnitude of the set “negative” ventilator elastance).

As lung recoil pressure is completely balanced by the ventilator pressure at this point, passive expiration will still not ensue even though the inspiratory effort may be long over. Therefore, besides tidal volume limits, an airway pressure limit and an inflation time limit should always be in place during PAV/RMU (Schulze et al. 1998a).

Full compensation of pulmonary resistance (when negative ventilator resistance equals pulmonary resistance in magnitude) induces sinusoidal oscillations of the respiratory system near its resonant frequency. This phenomenon can be explained by electrical or mechanical analogies of the respiratory system. The amplitude of the oscillations increases with higher gains of resistive unloading so that a variant of high-frequency oscillatory ventilation near the resonant frequency may be generated (Schulze et al. 1991).

Effect of Endotracheal Tube Leaks

A leak around the endotracheal tube will be measured as inspiratory airflow and volume by the pneumotachograph that is mounted at the endotracheal tube adapter. In the PAV/RMU modes, this will cause a rise in airway pressure out of proportion to the airflow and volume entering the lung. In case of a substantial leak, the ventilator pressure will rise rapidly to the set pressure limit and then fall to the PEEP level and may rise again repetitively. However, the leak component of the airflow signal can be estimated by the ventilator so that the airway pressure changes can then be based on a corrected flow signal (Fig. 8.26). With appropriate algorithms, PAV/RMU devices for infants can perform satisfactorily in the presence of variable leaks of up to 20–30 % of the tidal volume.

8.1.3.3.2.7 Studies on PAV/RMU in Small

Animal Species and Infants

PAV/RMU has been extensively studied in small adult and newborn animals with normal lungs and in various models of neonatal lung diseases such as surfactant deficiency and meconium aspiration. A clinical study on preterm infants compared PAV to assist control and to conventional mechanical ventilation in a crossover design in 36 infants (body weight 600–1,200 g) with mild

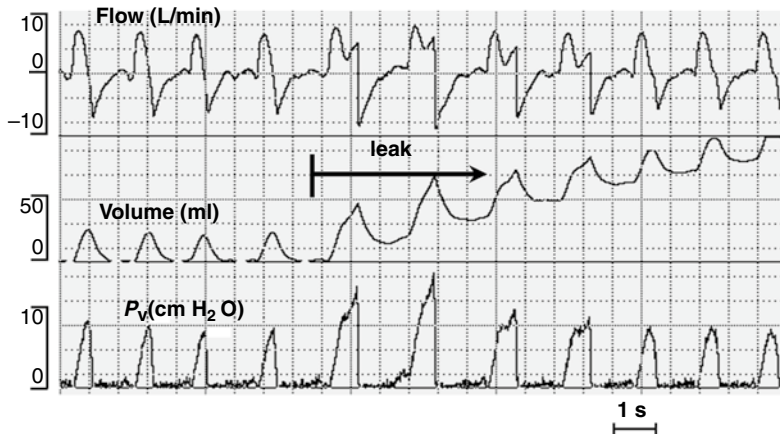


Fig. 8.26 Sudden opening of a substantial endotracheal tube leak during proportional assist ventilation: Note that the ventilator pressure increases during inspiration out of proportion with the tidal volume signal and reaches the upper ventilator pressure limit. Four inflation

later, however, it returns to its pre-leak contour although the leak persists. An algorithm in the ventilator software recognizes the air leak, calculates its average size, and subsequently subtracts leak flow from the measured total inspiratory airflow. Recording from a normal piglet

to moderate acute respiratory illness (Schulze et al. 1999a). Short-term physiological outcome variables were evaluated. During PAV, required mean airway pressures and transpulmonary pressures were lower at equivalent oxygen exposure, equivalent pulmonary oxygen uptake, and a similar CO_2 removal rate. Under the strictly controlled conditions of the study, PAV appeared safe and at least as effective as the comparison conventional modes. Infants on PAV typically showed a “fast and shallow” respiratory pattern, with respiratory rates about between 50 and 80/min. Tidal volumes were usually smaller than 5 mL/kg. Because preterm infants with their immature renal function are often slightly acidotic, it had been suspected that infants might hyperventilate when enabled to do so with PAV. This, however, was not corroborated. PAV was subsequently investigated in 22 chronically ventilator-dependent preterm infants (mean birth weight 705 g) in a crossover study design with conventional patient-triggered ventilation (Schulze et al. 2007). Ventilator pressure cost of ventilation was statistically significantly lower during PAV compared to the conventional triggered control mode. Recently, improved adaptive backup ventilatory strategies for episodes of cessation of the respiratory drive and oxygen desaturation during PAV have been shown to be effective in preterm infants (Herber-Jonat et al.

2006). In addition, PAV has been used in studies investigating various aspects of the regulation of spontaneous breathing in preterm infants. However, PAV has not been formally evaluated as the initial and sole ventilatory modality in preterm infants with respiratory failure. Also, its utility in infants with other types of pulmonary or cardiac diseases has not been studied.

8.1.3.3.3 Adaptive Support Ventilation

Jean-Michel Arnal

Educational Aims

- Understand the physiological background and the principle of functioning.
- Know how to set, adjust, and monitor.
- Review the evidences for passive and active breathing patients in adult and pediatric.

8.1.3.3.3.1 Adaptive Support Ventilation

Introduction

Closed-loop ventilation modes are designed to adjust automatically some settings based on measurement obtained from the patient. A lot of closed-loop control of ventilation (Saxton

and Myers 1953; Frumin 1957; Mitamura et al. 1971; Coles et al. 1973; Schulz et al. 1974; Coon et al. 1978; East et al. 1982; Ohlson et al. 1982; Chapman et al. 1985; Rudowski et al. 1991), mechanical pump (Younes 1992; Dojat et al. 1992; Iotti et al. 1996), oxygenation (Yu et al. 1987; East et al. 1991), or combined systems (Mitamura et al. 1975; East et al. 1986; Strickland and Hasson 1991; Waisel et al. 1995) have been described, but few of them are commercially available. Adaptive support ventilation (ASV) is at the present time the only closed-loop ventilation mode to accommodate both for passive and active breathing patients. Based on continuous measurement of pulmonary mechanics, it is conceptually capable of following the disease process automatically and delivers a breath pattern adapted to the respiratory system mechanics.

Japanese authors were the first to report adjustment of tidal volume (V_T) and respiratory rate (RR) to control CO_2 and to introduce work of breathing (WOB) as a parameter to select the breath pattern (Mitamura et al. 1971, 1975). Laubscher et al. carried the idea further and made the transition from passive to active ventilation an integral part of their adaptive lung ventilation (ALV) and its commercial implementation of ASV (Laubscher et al. 1994a). Although ASV has been available for more than 10 years, clinical experience reported was mainly in the adult population, and pediatric experience remains scarce.

Principles of ASV

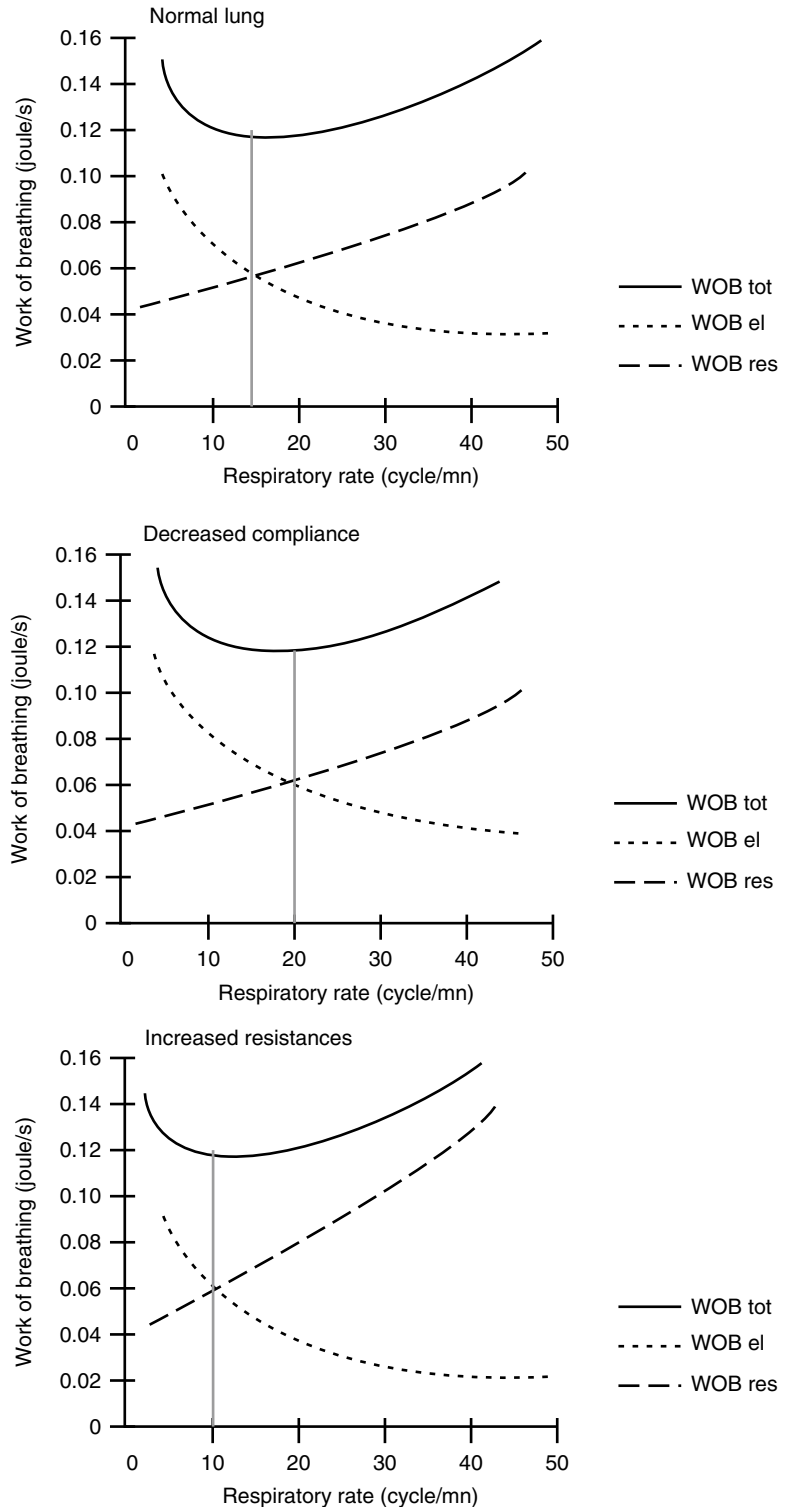
The basic principle of ASV stems from the work by Otis et al. (1950) and Mead (1960) demonstrating that, for a given level of alveolar ventilation, there is a particular RR that minimize the WOB. This optimal RR is the best compromise between elastic WOB and resistive WOB (Fig. 8.27) and depends on the minute volume (MV), the expiratory time constant (RC_{exp}), and the dead space (V_D). To initiate ASV, the clinician sets the patient's predicted body weight (PBW) and the percentage of minute ventilation (100 % being equal to 100 mL/kg PBW/min in adult patients). V_D is computed by the Radford

monogram at 2.2 mL/kg PBW. The ventilator then delivers five test inflation to determine RC_{exp} by analysis of the expiratory flow–volume curve (Brunner 2001; Brunner and Iotti 2002; Laubscher et al. 1994b; Brunner et al. 1995; Lourens et al. 2000). Thereafter, the ventilator compute the target V_T and RR, and mechanical ventilation starts using an interbreath negative control of V_T and RR to drive the patient's breath pattern to the target V_T and RR (Brunner 2002). In passive patients unable to trigger a breath, the ventilator generates pressure-controlled inflation and automatically adjusts the inspiratory pressure (P_{insp}) and timing to achieve the target V_T and RR. In active patients able to trigger a breath, the ventilator switch to pressure support inflation, automatically adjusting P_{insp} to achieve the target V_T , and it delivers additional pressure-controlled inflation if the patient's RR is below the target RR. During the maintenance, RC_{exp} is estimated on a breath-by-breath basis to reassess the target and adjust P_{insp} , $I:E$ ratio, and mandatory RR to maintain the target MV and RR within a frame designed to avoid both rapid shallow breathing and excessive inflation volumes. These safety limits to prevent markedly abnormal ventilator settings are automatically determined or can be manually adjusted. The limits are (min–max) as follows: inspiratory pressure (5 cm H_2O above PEEP to 10 cm H_2O below set P_{max}), V_T (4.4 mL/kg PBW to 22 mL/kg PBW), mandatory respiratory rate (5/min to 20/ RC_{exp} /min), inspiratory time (0.5–2 s), expiratory time (3 RC_{exp} to 12 s), and inspiratory/expiratory time ratio (1:4–1:1). The rather high value of 22 mL/kg PBW for the upper limit of tidal volume can be set at a lower level to avoid lung overdistension by setting P_{max} .

Settings, Adjustments, and Monitoring

At initiation, clinician has to set MV by setting PBW and %MV. It is crucial to set properly the PBW and not the actual body weight. A large discrepancy between PBW and set body weight may result in large V_T delivered (Dongelmans et al. 2008). Usually, %MV is set at 100 % as a starting point (110 % if an HME or heat and moisture exchanger is used on the ventilatory circuit).

Fig. 8.27 Principle of ASV. ASV is based on Otis' physiological work (Otis et al. 1950) which determined that for a given minute ventilation, resistive work of breathing (WOB) increases when respiratory rate (RR) increases (*dotted line*). Reversely, elastic WOB decreases when RR increases (*dash line*). Thus, total WOB (resistive WOB + elastic WOB) (*plain line*) has a U shape with an optimal RR associated with the least WOB (*grey line*). *Upper panel* is for normal lung patients. *Middle panel* is the relationship between RR and WOB in decreased compliance patients (e.g., ARDS): the optimal RR is higher than normal lungs. *Lower panel* is the relationship between RR and WOB in increased resistances patients (e.g., asthma): the optimal RR is lower than normal lungs



Later, %MV is adjusted by 10–20 % according to the PaCO_2 measured on blood gas analysis. In addition, settings of PEEP, FiO_2 , P_{max} , inspiratory trigger sensitivity, rise time, and expiratory trigger sensitivity are required. In passive patient, monitoring is similar to the pressure control mode. Plateau pressure is estimated by P_{insp} if inspiratory flow reach zero at the end of inspiration, otherwise an end-inspiratory occlusion is required. Total PEEP is assessed by an end-expiratory occlusion maneuver, especially in asthmatic and COPD patients (Brochard 2002). In active patient, monitoring is similar to pressure support. P_{insp} required to reach the target V_T informs on the readiness to wean the patient. If the ASV screen shows that the patient's RR is far above the target RR, it means a high ventilatory drive that may require increasing the %MV in addition to the etiologic treatment (Wu et al. 2004) (Fig. 8.28). In all cases, monitoring of RCexp inform of the respiratory mechanics. The normal value for intubated adult patient is around 0, 75 s (Arnal et al. 2008). A longer RCexp suggests an obstructive disease (asthma, COPD, bronchospasm, etc.) if not an excess of secretion or an endotracheal tube kicking. A shorter RCexp suggests a restrictive disease either due to the lung (atelectasis, ARDS, etc.) or to the chest wall (morbid obesity, kyphoscoliosis, etc.).

Studies in Passive Condition

A multicenter trial tested the safety of ASV as compared to volume control mode (VC) in 48 passive adult patients (Iotti et al. 2005). In term of peak pressure, Pplat, and intrinsic PEEP, ASV was at least as safe as VC. Furthermore, in one-third of these patients, ASV was more effective than VC in clearing CO_2 . An observational study in a cohort of 243 adult patients with different lung conditions reported different V_T –RR combination delivered according to the respiratory mechanics. V_T delivered was 8.3, 9.3, and 7.6 mL/kg PBW for normal lung condition, COPD, and ARDS condition, respectively (Arnal et al. (2008). In ARDS patients, a bench study compared V_T and Pplat delivered by ASV versus a strict 6 mL/kg PBW strategy (Suleymanci et al. 2008). Result showed that in

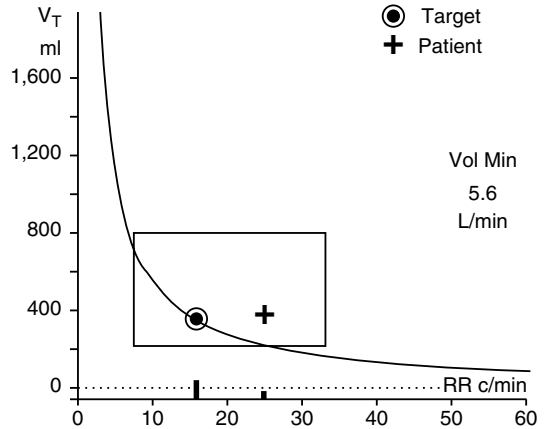


Fig. 8.28 The ASV screen displays respiratory rate (RR) versus tidal volume (V_T). In this example, minute ventilation (MV) set is 5.6 L/min. The curve represents all the V_T –RR combination to achieve the MV. The circle is the target calculated by the ventilator according to the expiratory time constant. The square is the safety window automatically calculated by the ventilator, which can be also manually adjusted. The cross is the actual breath pattern of the patient. In this case, the patient is actively breathing with a spontaneous RR above the target RR. In order to match spontaneous RR and target RR, clinician can increase the %MV which will increase the ventilatory support

the most severe cases of low compliance, high PEEP, and high MV, ASV was able to keep Pplat lower than the 6 mL/kg strategy. This is in favor of a good adaptation of the breath pattern delivered according to the respiratory mechanics with a V_T delivered below 6 mL/kg PBW for the most severe cases. A subsequent observational study focusing on 51 unselected ARDS patients confirmed the previous result with V_T delivered at 7.8 mL/kg PBW on the first day of mechanical ventilation correlated to the static compliance. In addition, Pplat was kept ≤ 28 cm H_2O during all the ventilation duration (Arnal et al. 2006). Two preliminary studies in large numbers of patient report the use of ASV in 98 % of ICU patients (Arnal et al. 2004) with a rate of failure of 3 % (Sviri et al. 2007). To resume, ASV can be used with safety in all conditions of passive ventilated ICU patient. The breath pattern selected is adapted to the respiratory mechanics and is in line with recommendations regarding protective ventilation strategy in ARDS patients (Yilmaz and Gajic 2008).

Studies in Active Condition and Weaning

In stable patients spontaneously breathing, the ASV algorithm will progressively and automatically reduce the inspiratory pressure as the patient's respiratory mechanics improve. A bench study determined that ASV effectively maintains minute ventilation and alveolar ventilation under various conditions of spontaneous ventilation, compliance, and airway resistances (Lawson et al. 2001). A physiological study in ten patients during early weaning with partial ventilatory support suggested an improvement in patient-ventilator interaction and reduced signs of dyssynchrony with ASV compared with SIMV-PS (Tassaux et al. 2002). Another physiological study in 14 adult patient during weaning phase showed that ASV and PSV behaved differently but ended up with similar pressure level facing acute changes in ventilatory demand by contrast to dual modes (volume-guaranteed pressure-control mode), in which an increase in ventilatory demand results in a decrease in the pressure support provided by the ventilator (Jaber et al. 2009).

Preliminary studies in adults suggest that ASV can simplify ventilator management and reduce the time to extubation in predominantly postoperative patient populations. Two RCTs involving 49 and 34 post-cardiac surgery patients, respectively, found that compared to protocols using SIMV and PS, ASV resulted in fewer changes in the ventilator settings from the ICU team providing care (Sulzer et al. 2001; Petter et al. 2003). Additionally, the first one noted that ASV resulted in significantly fewer high-inspiratory pressure alarms (Sulzer et al. 2001), while the second one also noted that ASV significantly reduced the duration of endotracheal intubation [3.2 (2.5–4.6) vs. 4.1 (3.1–8.6) h; $P=0.02$] and resulted in more fast-track successes (successful extubation at 6 h) (Petter et al. 2003). Two recent RCT performed in post-cardiac surgery patients found conflicting results (Gruber et al. 2008; Dongelmans et al. 2009). The first one included 50 patients after elective coronary artery bypass grafting and found earlier extubation associated with the use of ASV, without an increase in clinical intervention, when compared with pressure-regulated volume-controlled ventilation (Gruber

et al. 2008). The second one compared ASV with pressure support for the post-cardiac surgery weaning in 128 patients and did not find any benefit in terms of ventilation duration (Dongelmans et al. 2009). In all these study, the weaning protocol associated with the use of ASV interfere with the results.

Studies in Pediatrics

To test the response of ASV in small pediatric patients with a sizeable endotracheal tube leak, a bench study found that MV delivered was not affected by leaks as high as 50 % for patients whose PBW is 5 kg (Watson et al. 1999). From 10 to 20 kg, MV delivered is affected if leaks are above 25 %. A short-term crossover designed study compared ASV with SIMV in 13 children (mean age 2.3 years, actual body weight 12.3 kg) (Parret et al. 2000). Both V_T and peak pressure were decreased with ASV associated with an increase in inspiratory time and a decrease in expiratory time. At the present time, ASV can be used in children in the same way as in adult. In neonates, the experience is too scarce to recommend its use.

Limitations. The absolute contraindication of ASV is an important leak on the circuit as the monitoring of the V_T would be disturbed. Thus, ASV is currently not recommended in noninvasive ventilation and in case of bronchopleural fistula. ASV is more and more used around the world both in adult and pediatric population. Still, data are lacking concerning the weaning duration in ICU (beside postoperative patients), workload, cost, and outcomes especially in pediatrics.

Future Perspectives

The rational for using closed-loop ventilation is becoming stronger. It will become unavoidable in ICU aiming to achieve cost-efficiency, quality, and safety. The challenge is how to make that change effortless, friendly, and as fast as possible. Introducing novel graphical user interfaces and providing data displays that are pertinent, integrative, and dynamic will reduce

cognitive resources of the clinician and have the potential to make ventilation safer (Wysocki and Brunner 2007). They may be the key for adopting closed-loop ventilation in everyday practice. Furthermore, new closed-loop control will be integrated in the algorithm to control ventilatory pump and oxygenation.

including patient–ventilator synchronization, concept of diaphragm unloading, and settings of the NAVA level and PEEP

- To describe how NAVA could generate clinical benefits, already demonstrated or in future perspectives
- To present practical use of NAVA

Essentials to Remember

ASV is currently the only closed-loop ventilation mode available for both passive and active breathing patient. The algorithm selects automatically a V_T –RR combination associated with the least WOB with designed safety features. Initial settings and adjustments are simple. The monitoring is very similar to conventional ventilation modes. Clinical studies in adult ICU patients have shown a good adaptation of the breath pattern delivered in different lung condition without any safety issue. In some settings, ASV was associated with a faster weaning for post-cardiac surgery patients. Beside many potential advantages, data are still lacking, especially in pediatric population.

Mechanical ventilation can induce deleterious effects on lung parenchyma (Dreyfuss and Saumon 1998) or inspiratory muscles (Levine et al. 2008). Emerging evidence suggests that physiological and clinical benefits could be obtained by (1) maintaining spontaneous breathing during mechanical ventilation (Allen 2006; Putensen et al. 2006), (2) avoiding excessive respiratory support (Petrucci and Iacovelli 2007), and (3) reducing patient–ventilator asynchrony (Thille et al. 2006). Pneumatically triggered ventilation modes are universally used, but patient–ventilator synchrony remains poor in both adults and pediatric patients (Thille et al. 2006; Beck et al. 2004). In order to improve patient–ventilator synchrony, Sinderby et al. described in 1999 (1999) the neurally adjusted ventilatory assist (NAVA), a mode that provides a ventilatory support triggered by and proportional to the electrical activity of the diaphragm (EAdi). NAVA has first been developed and extensively evaluated in healthy volunteers and animals. It has recently become available on the Servo ventilators (Maquet Critical Care, Solna, Sweden) and preliminary experiences of NAVA in ICU patients commence to be reported. In this chapter, the NAVA theoretical concept will first be explained. The potential benefits and problems with NAVA will then be discussed, from theoretic basis to clinical data when available. Last, practical considerations and future perspectives will be presented.

8.1.3.3.4 Neurally Adjusted Ventilatory Assist (NAVA)

Guillaume Emeriaud

Educational Aims

- To highlight the importance of the electrical activity of diaphragm (EAdi), its physiological relevance, and its recording method
- To describe the global concept of neurally adjusted ventilatory assist (NAVA)
- To discuss specific points (benefits or problems) concerning NAVA, from the theoretic basics to the clinical data,

8.1.3.3.4.1 Theoretical Aspects

Electrical Activity of Diaphragm (EAdi)

Unlike the conventional ventilatory modes which adapt the assistance to airway pressure or flow, NAVA is adjusted by the neural drive

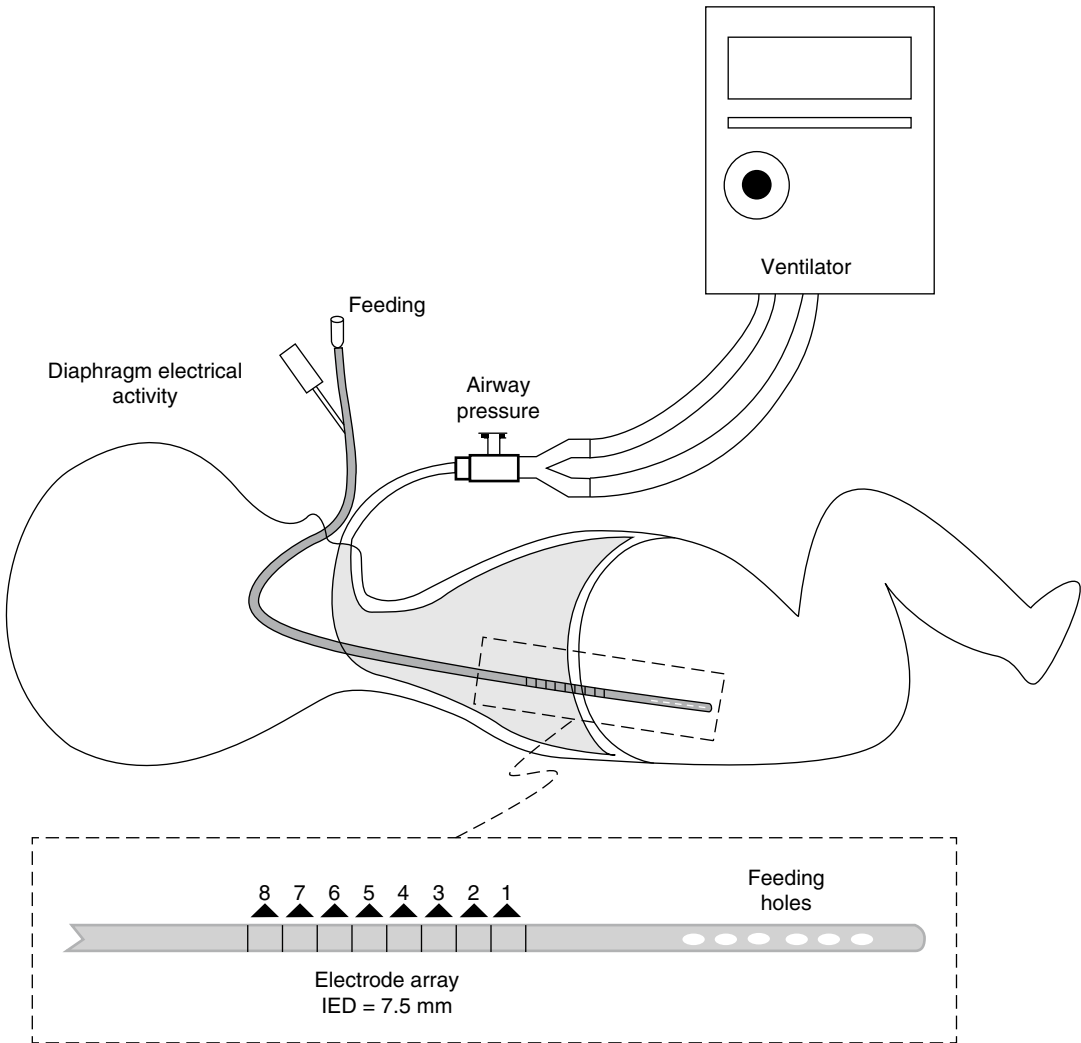


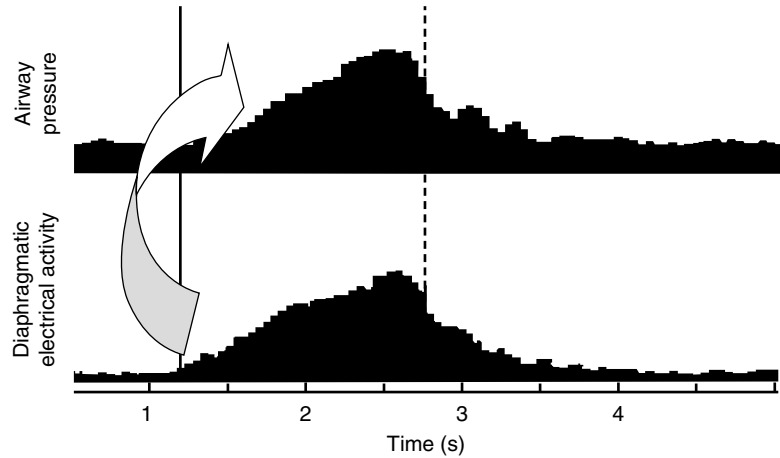
Fig. 8.29 Arrangement of the electrode array on the specific gastric catheter inserted in the lower esophagus

to the diaphragm. The key parameter is the EAdi, which is assumed to reflect the patient respiratory center demand. EAdi signal is continuously recorded using an array of nine miniaturized electrodes mounted on a conventional feeding tube positioned in the lower esophagus (Fig. 8.29). An automated method for online acquisition and processing of EAdi signal has been developed to obtain a high signal-to-noise ratio, to limit electrocardiogram influence, and to maintain an optimal muscle-to-electrode distance despite the diaphragm displacement. Briefly, a cross-correlation analysis of signals measured by each electrode pair permits to identify the

diaphragm position (along the array): The most negative correlation value is obtained from the electrode pairs located on either side of the diaphragm (Beck et al. 1996; Sinderby et al. 1997). The signals given by the electrode pairs the closest to the diaphragm are subtracted and filtered, and the remaining heart artifacts are suppressed by replacement (Sinderby et al. 1995, 1998). The final EAdi signal is transferred to the ventilator.

EAdi reflects the respiratory center demand, as illustrated by the EAdi increase observed when the respiratory load is artificially augmented, or in patients with restrictive or obstructive respiratory diseases (Sinderby et al. 1998). Good quality

Fig. 8.30 EAdi and airway pressure during a single breath with NAVA. The ventilatory assist is triggered when EAdi exceeds a threshold level (vertical solid line). The magnitude of inspiratory support is proportional to EAdi, with a modifiable gain factor called the NAVA level (arrow). The inspiratory interruption occurs when EAdi decreases below 70 % of peak EAdi (vertical dashed line)



EAdi signals have been successfully recorded in healthy volunteers, critically ill adult patients, pediatric patients including premature infants (Beck et al. 2009; Emeriaud et al. 2006), and small animal species (Allo et al. 2006). Adequate EAdi has also been recorded in patients with severe neuromuscular disease (Beck et al. 2006).

NAVA Principle

During NAVA, the ventilatory assist is triggered when EAdi exceeds a threshold level (Fig. 8.30). The magnitude of the mechanical support during inspiration is adapted every 60 ms, corresponding to the EAdi multiplied by a proportionality factor that can be selected, called the NAVA level. Inspiratory support is interrupted when EAdi decreases below 70 % of the peak EAdi, and the selected PEEP is then applied. Experiences of short periods (maximum 8 h) of ventilation with NAVA have been reported in healthy volunteers (Moerer et al. 2008), critically ill adult patients (Brander et al. 2009a; Colombo et al. 2008; Spahija et al. 2010), pediatric patients (Breatnach et al. 2010; Bengtsson and Edberg 2010), premature infants (Beck et al. 2009), and small animal species (Beck et al. 2008; Lecomte et al. 2009).

8.1.3.3.4.2 Specific Advantages and Difficulties with NAVA

Patient–Ventilator Synchronization

One major advance with NAVA concerns the patient–ventilator synchronization. The electrical activation of the diaphragm precedes its contraction and the modification of pressure or flow in

the respiratory circuit; cycling-on delay is intrinsically lower with NAVA than with conventional ventilation based on pneumatic triggering. An important point is that this synchrony should not be affected by the presence of leaks nor by unfavorable mechanical conditions like overdistension with intrinsic PEEP.

The improvement in patient–ventilator synchrony has been confirmed in lung-injured rabbits, with lower trigger delay and fewer non-assisted inflation with NAVA than with pressure-support ventilation (PSV) (Beck et al. 2007). In adult critically ill patients, NAVA was associated with lower asynchrony than PSV, particularly at high level of assistance (Colombo et al. 2008; Spahija et al. 2010); shorter delays were also observed with NAVA for both triggering the assist and cycling off (Spahija et al. 2010). In 7 premature infants (weight 976 ± 249 g), trigger delays were also similar with NAVA or PSV, but the cycling off was more synchronous in NAVA (Beck et al. 2009). Importantly in the same study, the trigger and cycling-off delays in NAVA were not altered after extubation (Beck et al. 2009). In pediatric patients, the synchrony has been less evaluated, but it has been shown that the neural triggering precedes the pneumatic triggering in more than 2/3 inflation during NAVA (Breatnach et al. 2010; Bengtsson and Edberg 2010).

During noninvasive helmet ventilation, an improved patient–ventilator synchrony has also been demonstrated in volunteers (Moerer et al. 2008).

Concept of Diaphragm Unloading

The patient–ventilator synchrony is also improved with NAVA in a second dimension: The assist is delivered proportionally in response to the patient respiratory center demand. This relation relies on the concept of unloading the diaphragm during the period of increased respiratory load, in order to prevent a diaphragm fatigue. This concept is quite different than other conventional modes used in pediatric and neonatal patients, like pressure support with volume guarantee, assist-control ventilation, and volume assist. With these modes, when the patient efforts augment, the ventilator progressively decreases its assistance after a few cycles. This can be considered an indication of weaning readiness, but this can also augment the diaphragm fatigue or the oxygen consumption if the situation is prolonged. In contrast, an increase in EAdi during NAVA ventilation is considered like an augmented demand, and the response is a higher assistance. This concept has first been validated in healthy volunteers, with the adjustment of pressure-support amplitude in order to maintain EAdi in an optimal target during exercise (Spahija et al. 2005). Studies in adult (Brander et al. 2009a; Colombo et al. 2008), pediatric (Breatnach et al. 2010; Bengtsson and Edberg 2010), and premature patients (Beck et al. 2009) have confirmed the clinical applicability of NAVA concept. However, the clinical benefit of this concept remains to be demonstrated.

The adjustment of the ventilatory assist to the patient demand implies that this demand is continuously appropriate. Feasibility of NAVA may be impaired in particular during profound sedation. The minimal level of sedation which permits NAVA ventilation has to be studied, but individual evaluation can be done with the monitoring of EAdi during conventional ventilation. A particular concern for pediatric physicians is the immaturity of the central respiratory centers, especially during the neonatal period. Apneas are detected during NAVA, and backup ventilation is activated. However, periodic breathing risks inducing periods of low ventilation. This phenomenon remains to be evaluated, and alarms of minimal ventilation have to be set with caution.

Nava Level Setting

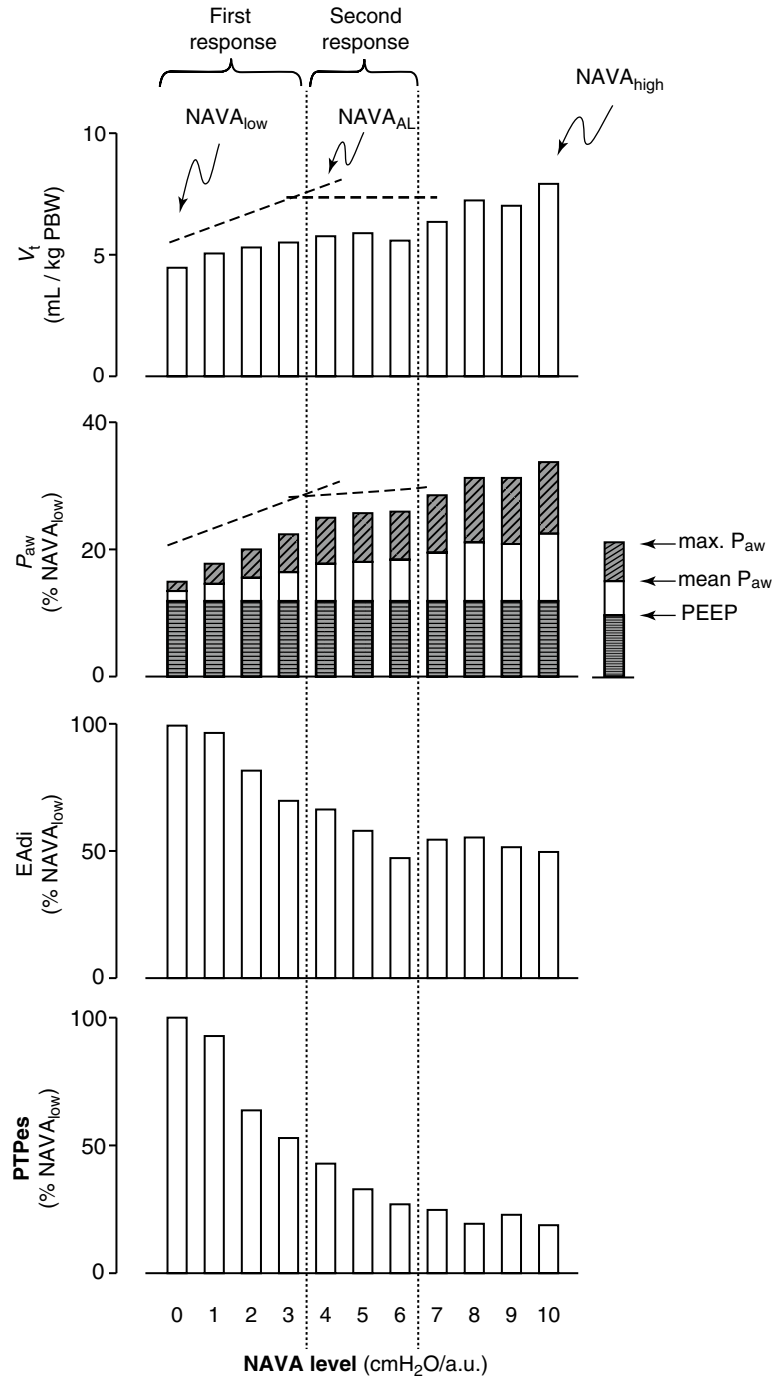
The NAVA level is the main ventilator setting during NAVA. This proportionality factor permits to augment the ventilatory support when EAdi increases. There is a theoretic risk of excessive pressure or tidal volume. However, it has been well established in human volunteers (Beck et al. 2001), in animals (Allo et al. 2006; Beck et al. 2008; Lecomte et al. 2009), and in adult patients (Brander et al. 2009b; Colombo et al. 2008; Spahija et al. 2010) that a downregulation prevents excessive ventilation when NAVA level is elevated. When the NAVA level is titrated from zero to high level in cases of acute lung injury (Brander et al. 2009b; Lecomte et al. 2009), a two-phased response is observed (Fig. 8.31). At lower levels, airway pressure and tidal volume progressively increase, unloading the diaphragm as illustrated by a decrease of EAdi which probably return to its normal level. When the NAVA level is further augmented, the EAdi decreases further, illustrating the lower demand, and the inspiratory pressure and tidal volume will plateau. In animals, when NAVA level is at the breakpoint between the two response phases, esophageal pressure, EAdi, and PaCO₂ are similar to their baseline normal values.

The ventilatory support adjustment to the patient demand does not result in excessive ventilation. It has been shown, in premature infants (Beck et al. 2009) as in adults (Brander et al. 2009a; Colombo et al. 2008), that patients with acute lung injury ventilated with NAVA spontaneously chose a protective tidal volume (6–7 mL/kg). In pediatric patients, peak inspiratory pressures were lower during NAVA as compared to PSV, with similar minute ventilation (Breatnach et al. 2010; Bengtsson and Edberg 2010). It is however possible that very high NAVA levels induce transiently high tidal volumes or pressures, and corresponding alarms should be activated.

PEEP Setting

PEEP setting remains a challenge in intensive care. Two particularities have to be addressed with NAVA. The first point concerns the intrinsic PEEP and hyperinflation. With conventional ventilation, patients have to overcome the intrinsic

Fig. 8.31 Changes in tidal volume (V_t), mean airway pressure (P_{aw}), EAdi, and esophageal pressure–time product (PTPes) during NAVA level titration in a patient. A biphasic response can be observed. At low level of assistance (NAVA low), P_{aw} and V_t increase progressively with the NAVA level, with a progressive reduction of EAdi illustrating the diaphragm unloading. Above the breakpoint (considered the adequate NAVA level, NAVA_{AL}), V_t and P_{aw} reach a plateau despite NAVA level increase, due to the downregulation on EAdi (From Brander et al. 2009a, published with permission)



PEEP before the respiratory effort can be detected. To lower this trigger delay, it is recommended to add an external PEEP. In NAVA, the trigger delay should not be altered by overdistension and this PEEP indication has probably to be reevaluated.

The second point concerns the tonic EAdi. In intubated infants, around 15 % of the inspiratory EAdi remain active at the end of expiration (Emeriaud et al. 2006). This tonic EAdi is probably involved in the control of the end-expiratory lung volume, by braking

the expiratory flow. When PEEP is lowered to zero, tonic EAdi increases (Emeriaud et al. 2006; Beck et al. 2008), suggesting that tonic EAdi reflects the patient's effort to maintain an appropriate end-expiratory lung volume. It can be hypothesized that high levels of tonic EAdi correspond to insufficient levels of PEEP. This remains to be evaluated, but tonic EAdi may become a valuable tool for the adjustment of PEEP in the future.

Clinical Benefits

It has to be noticed that no data concerning periods of ventilation superior to eight hours have yet been published. The feasibility of long-term ventilation with NAVA appears good but has to be confirmed, and in particular the stability of EAdi recording.

The improvement in patient-ventilator synchrony is well established with NAVA. The clinical benefits resulting from this synchrony in terms of comfort, sleep quality, sedative use, and ventilation duration have to be evaluated with long-term ventilation periods with NAVA.

NAVA seems also to generate a "safe" ventilation with low tidal volumes. This aspect has recently been confirmed in a study with lung-injured rabbits, in which lower tidal volumes, lower airway pressures, and better $\text{PaO}_2/\text{FiO}_2$ were observed with NAVA as compared to protective conventional ventilation (6 mL/kg), with similar prevention of ventilator-induced lung injury markers (Brander et al. 2009a).

NAVA seems also to augment the respiratory variability (Schmidt et al. 2008). Respiratory variability is likely beneficial in ICU patients (Wysocki et al. 2006) and this effect of NAVA will have to be studied as well.

8.1.3.3.4.3 Practical Considerations

NAVA is available on the Servo ventilators (Maquet Critical Care, Solna, Sweden). All the preparation steps are conducted while the patient breathes on its preceding conventional mode. The first step is the insertion of the special gastric catheter. The correct positioning of the catheter is based on pre-calculated distance of insertion and confirmed using a specific window on the ventilator where the signals of four

electrode pairs are displayed. The catheter is correctly positioned when the blue diaphragmatic signals appear mostly in the two middle tracings. Once a correct EAdi signal is displayed in the lower part of the screen, the second step is the setting of the NAVA level. This is generally achieved from a special function which permits to display both actual airway pressure (in conventional mode) and the estimated airway pressure that would result from NAVA ventilation. The NAVA level can be adapted in order to produce the desired pressure. An alternative (but more complex) way to set the NAVA level is to use the titration method described above and in Fig. 8.31. At that point, the NAVA mode can be activated after accurate selection of alarm levels (for maximal pressure, and minimal and maximal minute ventilation).

Of note, the ventilatory assist is triggered by the first activated trigger (EAdi or pneumatic). In case of loss of EAdi signal (e.g., displacement of the tube), pressure-support ventilation will be activated. It is therefore important to correctly set the pressure-support settings. A backup ventilation has also to be set (apneas).

Future Perspectives

NAVA is a new ventilation mode that will probably strongly modify the ventilation practice in intensive care. First experiences with NAVA have only recently been published, and most of the potential benefits are to be studied. Some future perspectives have been mentioned above; the most important one concerns the evaluation of clinical benefits with long-term NAVA. The selection of the patients who will best benefit from NAVA has also to be established. The development of NAVA in noninvasive context seems of paramount importance as well, as this situation is usually associated with a very poor patient-ventilator synchrony in pediatric patients (Essouri et al. 2005). Another perspective relies on the utility of the EAdi signal as a monitoring tool, which reflects very interestingly the patient respiratory center demand.

Essentials to Remember

- EAdi is an essential parameter in NAVA, which reflects the patient respiratory center demand. It is continuously recorded with an array of electrodes mounted on a specific gastric tube and with a standardized and automated signal processing algorithm.
- During NAVA, the patient–ventilator synchrony is optimized in two dimensions: (1) EAdi is used to trigger (on and off) the ventilatory assist, and (2) the assistance amplitude is proportional to EAdi (with a gain factor, called the NAVA level).
- The improved patient–ventilator synchrony with NAVA has been demonstrated in animals, in volunteers, and in adult and pediatric patients. The synchrony is not affected by large leaks – which could be highly valuable for noninvasive ventilation – nor by altered respiratory mechanics like overdistension.
- In contrast with other ventilation modes, when the respiratory drive augments in NAVA, the ventilatory assistance is increased. This concept of diaphragm unloading is not associated with excessive ventilation. The tidal volume spontaneously “chosen” by the patients is 6–7 mL/kg in both pediatric and adult patients.
- EAdi signal could also be used as a monitoring tool, reflecting the respiratory center demand. The tonic EAdi level may reflect the appropriateness of the PEEP level.
- Clinical benefits of long periods of ventilation with NAVA have to be evaluated.

8.1.3.4 Bi-level and Airway Pressure Release Ventilation

Mark J. Heulitt and Ronald C. Sanders Jr.

Educational Aims

- To understand the physiological principles associated with airway release ventilation/bi-level
- To understand the indications and contraindications of its use
- To understand how settings are manipulated to effect oxygenation and ventilation

8.1.3.4.1 Introduction

For the purpose of this chapter, we will use the terms airway pressure release ventilation (APRV) and bi-level interchangeable. These modes do differ according to the type of support allowed during the spontaneous inflation, with bi-level incorporating the option of pressure-support in the airway pressure waveform to augment spontaneous breathing. This discussion will be limited to these two modes and not include as reported modes such as BIPAP, IMPRV, and intermittent CPAP. These modes are relatively new, released in the early 1990s (Downs and Stock 1987; Stock et al. 1987), with no studies demonstrating its use reducing mortality or morbidity in ARDS, but has demonstrated improvement in gas exchange at lower airway pressures (Rasanen et al. 1987; Stock et al. 1987). The fundamental principles of both modes differ from conventional ventilation in regard to the starting point of the breath and where within the breath cycle spontaneous breathing can occur. Unlike conventional mechanical ventilation where the breath begins at a baseline pressure and then pressure is elevated to deliver a tidal volume, the APRV breath begins at an elevated baseline pressure and follows with a deflation from high pressure to deliver the tidal volume. Further, and

Table 8.7 Airway pressure release ventilation parameters

Term	Definition	Unit of measure
Pressure high (P_{High})	Baseline airway pressure level Higher of two airway pressures	cm H ₂ O
Pressure low (P_{Low})	Airway pressure level resulting from pressure release The lower of the two airway pressures	cm H ₂ O
Time high (T_{High})	Length of time for which P_{High} is maintained	Seconds
Time low (T_{Low})	Length of time for which P_{Low} is maintained	Seconds
Mean P_{aw}	$\frac{(P_{\text{High}} \times T_{\text{High}}) \pm (P_{\text{Low}} \times T_{\text{Low}})}{(T_{\text{High}} \pm T_{\text{Low}})}$	cm H ₂ O

more importantly, spontaneously breathing in contrast to conventional ventilation can occur at either the high-pressure or low-pressure levels. When spontaneously breathing is not present, APRV is not different from conventional time-cycled, pressure-controlled ventilation (Stock et al. 1987; Baun et al. 1989).

8.1.3.4.2 Definition

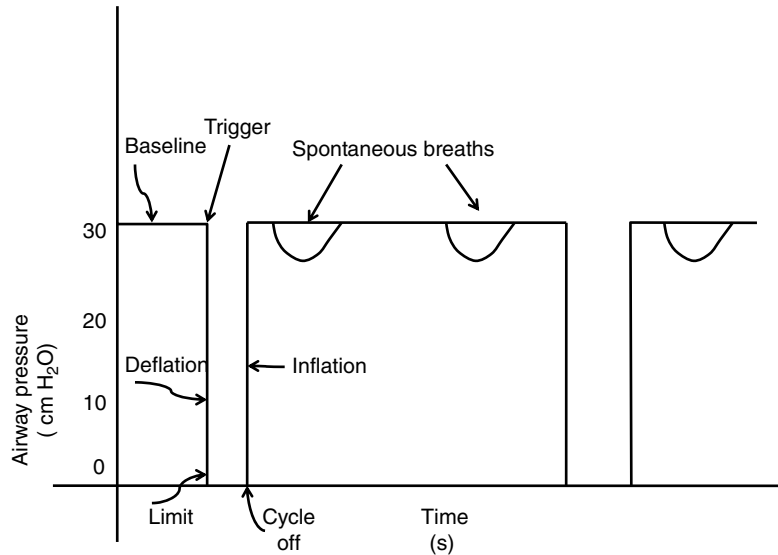
Practically APRV can be described as the application of continuous positive airway pressure (CPAP) with regular, brief intermittent releases of the airway pressure (Rasanen 1994; Burchardi 1996). However, unlike CPAP, APRV facilitates both oxygenation and CO₂ clearance. It is best described using Chatburn criteria (Chatburn and Primiano 2001), as a time-triggered, pressure-limited, time-cycled mode of mechanical ventilation. Theoretically, APRV is capable of complete support in the apneic patient or augmentation of alveolar ventilation in the spontaneously breathing patient. Table 8.7 summarizes the terms utilized in APRV. The degree of ventilatory support with APRV is determined by the duration of the two CPAP levels and the mechanically delivered tidal volume. Even though the terms can be confusing between manufacturers and publications, certain terms and principles are the same. These terms include measures of pressure and time: pressure high (P_{High}) the upper CPAP level analogous to MAP, pressure low (P_{Low}) is the lower

pressure setting, time high (T_{High}) is the inspiratory time or phase for the high CPAP level (P_{High}), and time low (T_{Low}) is the release time allowing for CO₂ elimination (Sydow et al. 1994). P_{High} is the higher of the two airway pressure levels and is the pressure at baseline. The pressure resulting from the pressure release is P_{Low} . T_{High} corresponds with the length of time which P_{High} is maintained; T_{Low} is the length of time for which P_{Low} is held or the time airway pressure is released (Fig. 8.32).

8.1.3.4.3 Physiological Effects

Since one of the potential advantages of APRV is to increase the time patients spend breathing spontaneously, we need to review the theoretical advantages of allowing patients to breathe spontaneously during mechanical ventilation. It has been demonstrated that spontaneous breathing provides ventilation to dependent lung regions that get the best blood flow, as opposed to PPV with paralyzed patients (Froese 1974). During spontaneous respiration, there is improved ventilation–perfusion by preferentially ventilating the peri-diaphragmatic regions that receive disproportional blood flow. This effect may vary with the intensity of the breathing efforts and the vigor of the expiratory muscle activity (Kleinman et al. 2002). In patients with ARDS, arterial hypoxemia has been explained by the intrapulmonary shunting due to alveolar collapse in the

Fig. 8.32 Airway pressure release ventilation differs from conventional modes because trigger initiates a drop in airway pressure rather than a rise. The amount of pressure changes will be the limit. The cycle off will occur because of time. Airway pressure then returns to the baseline



dependent regions of the lungs demonstrated on computed tomography (CT) (Gattioni et al. 1986). These changes appear to improve with less atelectasis and increased end-expiratory lung volumes as seen in end-expiratory CT of the lungs in experimental ARDS in animals breathing spontaneously in APRV (Wrigge et al. 2003). It has been suggested that the recruitment demonstrated during spontaneous breathing during APRV may be caused by an increase in transpulmonary pressure secondary to a decrease in pleural pressure (Henzler et al. 2004). These effects would lead to reduced atelectasis.

Both animals in experimental models and patients with ARDS breathing spontaneously on APRV have demonstrated improvement in intrapulmonary shunting and arterial oxygenation (Putensen et al. 1999, 1994a, b). Both these settings with improved arterial oxygenation and less atelectasis, thus improved pulmonary compliance, are indicative of lung recruitment. It is important to note that in patients these changes may progress over a period of time and not be instantaneous (Putensen et al. 1999).

Mechanical ventilation with a positive-pressure breath can have detrimental effects on the patient's cardiovascular status, especially in normo- and hypovolemic patients. This detrimental effect causes decreased stroke volume, cardiac output, and oxygen delivery

due to a reduction in right and left ventricular filling. Consequently, any type of ventilatory support that could cause a reduction of intrathoracic pressure would promote venous return to the heart and would reverse these detrimental effects. Reduction in intrathoracic pressure is seen in patients (Putensen et al. 1999; Sydow et al. 1994) and animals breathing spontaneously. Thus, these results would suggest that one should use lower PIPs in order to maintain oxygenation and ventilation without compromising the patient's hemodynamics (Sydow et al. 1994).

8.1.3.4.4 Clinical Applications

There is little direction on the application of APRV or bi-level. There are theoretical principles within recommendations for protective lung strategy that can be applied to the use of these modes (Artigas et al. 1998; Heulitt et al. 1995; Heulitt and Desmond 1998). First, the clinician must choose initial settings; in these examples we will use examples from Bi-vent, but the principles are the same with other manufacturers. APRV can provide full or partial ventilatory support with low peak airway pressure.

Proper application of APRV requires adjustment of CPAP to a level that results in optimum pulmonary gas exchange and lung mechanics. First select settings for P_{High} , T_{High} , and T_{PEEP} . For P_{High} in adults, this would be the plateau pressure

Table 8.8 Strategies used in APRV to change PaO_2 and PaCO_2

	PaO_2	PaCO_2
Increase	1. Increase FiO_2 2. Increase MAP by increasing P_{High} in 2 cm H_2O increments 3. Increase T_{high} slowly (0.5 s/change) 4. Recruitment maneuvers 5. <i>Maybe</i> shorten T_{PEEP} (T_{low}) to increase PEEPi in 0.1 s. increments (this may reduce V_T and affect PaCO_2)	1. Increase T_{high} (fewer releases/min) 2. Decrease P_{High} to lower delta pressure
Decrease		1. Decrease T_{High} 2. Increase P_{High} to increase delta pressure and volume exchange (2–3 cm H_2O/change) 3. Check T_{low}. If possible, increase T_{low} to allow more time for “exhalation”

or mean airway pressure in pediatrics. Typically this setting would be about 20–25 cm H_2O . In larger patients with P_{plateau} at or above 30 cm H_2O , it is recommended to set it at 30 cm H_2O . It is important to recognize that overdistension of the lung must be avoided. There is no agreement on what the maximum P_{High} should be, but high settings may be expected in patients that have morbid obesity and decreased thoracic or abdominal compliance (ascites).

For T_{High} the inspiratory time (T_{high}) is set at a minimum of 2.0 s in children and about 4.0 s in older patients. T_{high} is progressively increased (every 10–15 s) with a target being improved oxygenation. These changes should be progressed slowly, for example, 5 s T_{high} to 0.5 s T_{low} is a 10:1 ratio. So if you increase T_{High} to 5.5 s and T_{Low} to 0.5 s, this only changes the ratio to 11:1. In children use a T_{High} of 2 s. Target is oxygenation.

For release time, it has been proposed in patients with ARDS not to let exhalation go to complete emptying, i.e., do not let expiratory flow return to zero. Thus, regional auto-PEEP is a desirable outcome with Bi-vent. Set T_{PEEP} (T_{Low}) so that expiratory flow from the patient ends at about 50–75 % of peak expiratory flow. This can be determined by saving a screen on the ventilator and calculating the peak expiratory flow from it, or it can be estimated from the ventilator graphics. T_{PEEP} should be set to 0.5–0.8 s in adults and in 0.2–0.6 s in pediatric and neonatal patients. Another way to set it is to use one time constant ($\text{TC} = C \times R$). It is important to note that too long a

release time could cause the lung to collapse and interfere with the patient's oxygenation. Thus, it is important to monitor tidal volume and oxygenation so that sufficient time is allowed for reinflation of the lung and that the fall in mean airway pressure and transpulmonary pressure resulting from increasing the release rate does not impair arterial oxygenation. If alveolar ventilation is adequate, but average lung volume is insufficient to maintain oxygenation, the CPAP and the release pressure should be increased simultaneously in equal amounts until the desired effect on oxygenation is seen. In Table 8.8, there are specific recommendations in making ventilatory changes to affect oxygenation or ventilation.

8.1.3.4.5 Weaning

FiO_2 should be weaned first before any other parameters are weaned. A goal is to reduce FiO_2 to 0.50 or less. Weaning the support level of APRV may be accomplished by either reducing the frequency of pressure release or increasing the release pressure so that it is close to the level of CPAP. This is accomplished by manipulation of P_{High} and T_{High} . P_{High} is lowered 2–3 cm H_2O at a time to a goal to below 20 cm H_2O , and T_{High} will be lengthened in 0.5–2.0 s increments depending upon the patient tolerance to allow for 5 releases per minute. Thus, the patient is transitioned to CPAP with very few releases. It is important to add pressure support judiciously. Pressure support can be added to P_{High} to decrease work of breathing while avoiding

overdistension. It is important that P_{High} plus pressure support be maintained less than or equal to 30 cm H₂O. Patient needs to be monitored closely to document an increase for the patient's spontaneous rate to compensate for the APRV weaning.

8.1.3.4.6 Contraindications and Disadvantages

APRV and bi-level can be utilized in a diverse clinical population with acute respiratory failure. Due to the fact that the goal of APRV is to allow the patient to breathe spontaneously during a prolonged phase with increased intrathoracic pressure with a brief release of this pressure, conditions where these physiological effects may adversely affect the patient this mode must be used with caution.

Considerations of the advantages of APRV relates to the limitations of pressure-controlled ventilation, effects of airway and circuit resistance, decrease in transpulmonary pressure, and interference with spontaneous ventilation.

8.1.3.4.7 Pressure-Controlled Ventilation

The generation of tidal volume during APRV is primarily from generation of airway pressure. The magnitude is dependent upon adequacy of inspiratory and expiratory time associated with pressure-volume characteristics of the lungs. Thus, acute changes in pulmonary compliance will alter tidal volume, necessitating clinician-directed changes in settings. This limitation is not unique to APRV, but applies to all forms of pressure-controlled ventilation that has been demonstrated in patients with acute lung injury (Cane et al. 1991).

8.1.3.4.8 Effects of Airway and Circuit Resistance on Ventilation

In APRV, there must be adequate time to allow sufficient emptying of the lungs. There is no experience with the use of this mode in patients with obstructive lung disease. There is no reason to believe that the characteristics of this mode would be beneficial in patients with prolonged expiratory time constants. The rate of volume

changes in the lungs depends on their time constants that are a product of pulmonary compliance and resistance. In patients with significant airway obstruction, a longer release time may be required to allow adequate emptying of the lungs. It is important to note though that a longer release time may limit the mechanical minute volume that can be achieved by decreasing the maximum frequency of airway pressure release. Thus, one should use the shortest release time that allows expiratory flow to stop by the end of pressure release. Unfortunately, the optimum release time has not been established and must be adjusted depending upon the patient's clinical condition.

One final concern for neonatal and pediatric patients which is not clear is the role of APRV in patients with mixed conditions where there is both increased airway resistance and poor pulmonary compliance such as bronchopulmonary dysplasia.

8.1.3.4.9 Decrease in Transpulmonary Pressure

Another theoretical concern with APRV is the potential for a decrease in transpulmonary pressure and lung volume due to the fall in airway pressure. This effect could adversely impair oxygenation due to decreased lung volume affecting the ventilation-perfusion relationship. Reviewed studies utilizing APRV compared to conventional mechanical modes with similar mean airway pressure have not demonstrated a detrimental effect to oxygenation with patient during APRV (Garner et al. 1988; Valentine et al. 1991).

8.1.3.4.10 Interference with Spontaneous Breathing

Theoretically, there are distinct physiological advantages to patients breathing spontaneously on positive-pressure mechanical ventilatory support. During APRV, spontaneous breathing is unrestricted due to the design of the APRV circuit. However, the timing of spontaneous inflation could be problematic. For example, just as in nonsynchronized intermittent mandatory ventilation, inadvertent patient effort not timed to

inspiration or expiration could cause discomfort and increased work of breathing. These theoretical disadvantages have been demonstrated in lung models, but not in reported clinical trials.

Also to ensure spontaneous breathing by the patient, minimal sedation is utilized, and this could be detrimental in conditions where it is required to maintain the patients at levels of deep sedation. For example, in increased intracranial pressure where the goal is to reduce intracranial pressure and maintain cerebral perfusion pressure, intracranial pressure can be dependent on the transmitted pressure in the low-pressure, high-capacitance venous system; increased intrathoracic pressure may impair venous drainage from the brain and could worsen increased intracranial pressure and reduce cerebral perfusion pressure. For the clinician faced with a patient with acute hypoxic respiratory failure and traumatic brain injury, there must be a balancing between the needs to increase intrathoracic pressure to enhance lung recruitment and the possible adverse effects on the injured brain.

Other conditions where it may be contraindicated or unclear if there would be benefit are patients with neuromuscular disease or large bronchopleural fistula.

Future Perspective

Modifications to compensate for the limitations of APRV/bi-level have been proposed. Intermittent mandatory pressure release ventilation (IMPRV) is a combination of pressure-support ventilation, CPAP, and APRV. The mechanical cycle is patient triggered and begins with a pressure-support breath. Synchronization of spontaneous and mechanical inflation, breath-to-breath ventilatory support, and the ability to alter airway pressure both above and below a given level of CPAP are potential advantages over APRV. However, like APRV further study is required before it can be utilized routinely in infants and children.

Essentials to Remember

- APRV utilizes a release of airway pressure from an elevated baseline to simulate expiration. The elevated baseline facilitates oxygenation and the timed release aid in carbon dioxide removal.
- Advantages of APRV include lower P_{aw} for a given tidal volume, lower minute ventilation, limited adverse cardiovascular effects, potential decreased sedation use, and reduced need for neuromuscular blockade.
- Potential disadvantages are lung volume change with alterations in pulmonary compliance and resistance and the patient needs to be monitored closely for these changes.

8.1.3.5 Waveform Analysis

Mark Heulitt, Paul Ouellet, and Steve M. Donn

Educational Aims

- Understand the physiological principles responsible for gas delivery during positive-pressure mechanical ventilation.
- Understand the functional characteristics of mechanical ventilation including the control, phase, limit, and cycle variables.
- Understand the relationship between control and phase variables and their effect on displayed waveforms and calculated indices.

8.1.3.5.1 Introduction

Current ventilators have the ability to display breath-by-breath airway pressure, flow, and volume as a function of time necessary to overcome the elastic and resistive forces of the patient, ventilator, and circuit. It is important to note that of pressure, flow, and volume, only flow and pressure are measured and volume is calculated from flow by the ventilator. Further, current ventilators also may display calculated values from

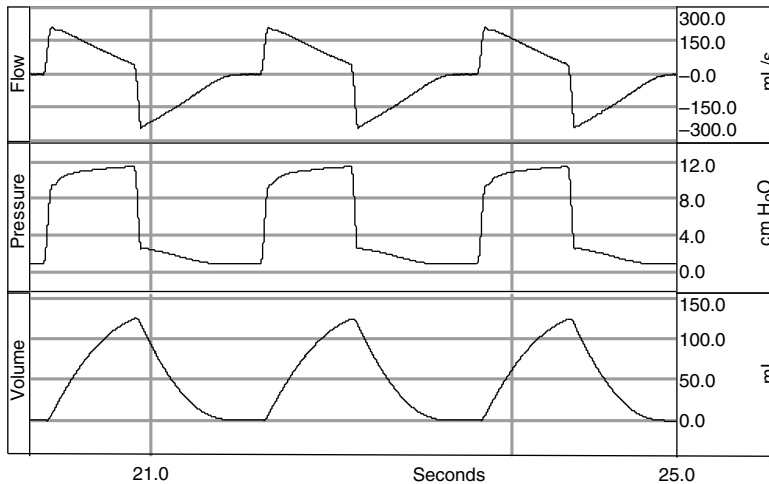


Fig. 8.33 Constant pressure normal; flow, pressure, and volume waveforms under normal conditions. During the inspiratory phase there is a rapid increase to peak inspiratory flow (PIF), and then flow decelerates through the inspiratory phase with an exponential decay to baseline.

During the expiratory phase peak expiratory flow (PEF) demonstrates a rapid decrease with again an exponential decay to baseline with end-expiratory flow being zero at the end of expiration

the above displayed parameters. Modern ventilators are equipped with a graphical display intended to allow the clinician to evaluate interactions between the mechanical ventilator and the patient. These interactions can be specific to the patient's disease state, the equipment (e.g., modality of ventilation being used), or the decisions of the clinician (e.g., adequacy of settings determined by the clinician). It is important for the clinician to recognize that the displayed and calculated parameters may be influenced by pre-determined factors not in their control, such as sampling frequency of the sensor and filtering of the displayed waveform. Also effects of adapters or filters placed in the ventilator circuit may influence the displayed and calculated parameters. In order for the clinician to evaluate and interpret values and waveforms displayed by the ventilator, the clinician must understand the physiological basis of those displayed values and waveforms.

8.1.3.5.2 Applied Physiology

The respiratory system, like most biological systems, is closely associated with exponential functions. An exponential function is a mathematical expression that describes an event where the rate of change of one variable is proportional to its magnitude.

An example, in a passive breath, expiratory flow will be higher at the beginning of expiration than at the end, as the lung volume decreases toward functional residual capacity (FRC).

There are various forms of exponential functions, but the two most important ones for the clinician in mechanical ventilation are the rise and the decay of exponential functions.

Rising exponential function expresses an increase of one variable as a function of time (flow, pressure, or volume versus time). A rising exponential expresses the behavior of a physical system, where the rate of change of one variable is proportional to its magnitude and a constant. In this relationship, the largest rate of change is always observed at the beginning of the event, and the smallest rate of change is always observed at the end of the event. This relationship is demonstrated in Fig. 8.33 of a flow–time waveform during a constant pressure modality. The change in flow is most rapid at the beginning of the breath and slows at the end. Exponential functions are often described with time constants. A time constant is a time interval. Short time constants imply a fast rate of change and long time constants reflect a slow rate. In a rising exponential function, after one time constant there is a rise of 63.3 % of its final value. After two time

constants it increases to 86.5 %, at three it is 95.1 %, and after four it increases to its final value 98.2 %. In mechanical ventilation, for practical purposes, an event is considered complete after three time constants (Rodarte and Rehder 1986).

Decaying exponential function expresses a decrease of one variable as a function of time (flow, pressure, or volume versus time). An example of this relationship can be seen with the pressure decrease during lung deflation in a passive expiration. Flow returns to a baseline during a passive expiration reflecting a negative decay function. This expression of a physical system is expressed where the rate is proportional to its magnitude only. Thus, the rate of change will always have the largest value at the beginning of the event and smallest at the end of the event. The rate of change is not constant over time as it is seen in rising exponential function.

During various forms of ventilation, the flow, pressure, and volume will vary with time as an exponential function. Depending on the modality of ventilation, compliance and resistance will affect both phases of each variable. During inspiration, flow and pressure patterns are directly related to the forces generated by the ventilator. Thus, the clinician can control flow and pressure through ventilation strategies in order to optimize ventilation according to the compliance and resistance of the patient's respiratory system. However, during expiration, flow, pressure, and volume patterns cannot be directly manipulated by the clinician, except for determining the duration of each cycle when using a control mode. Passive expiration is then directly governed by the elastic and resistive characteristics of the respiratory system. Thus, during mechanical ventilation, for practical reasons, the value of the expiratory time constant reflects characteristics of the global respiratory system, which consists of a multitude of zones each with different time constants. This is clearly evident in a disease state like ARDS where the lung pathology is nonhomogeneous with lung zones with different levels of compliance and resistance. Therefore, diseased zones will have shorter time constants than normal zones with normal compliance. However, ventilator strategies are directed at obtaining adequate

ventilation according to the global time constants of the total respiratory system. The respiratory system is governed by the laws of physics that involve the description of various dynamic forces involved in the movement of the system. In physiology, force is measured as pressure (P), displacement is measured as volume, and the relevant rate of change is measured as flow (average flow= $\frac{dV}{dt}$; instantaneous flow= $\frac{dV}{dt}$; the derivative of volume with respect to time). The pressure necessary to cause flow of gas into the airway and to increase the volume of the gas in the lung is the key component in positive-pressure mechanical ventilation. The volume of gas to any lung unit and the gas flow is related to the applied pressure by where R is the airway resistance and C is the lung compliance. This equation is known as the equation of motion for the respiratory system (RL Chatburn 1998 and Bates 1998). The applied pressure to the respiratory system measured at the inlet is the sum of the muscle pressures P_{mus} (pressure generated by the patient's spontaneous muscular forces) and the ventilator pressure (P_{Applied} pressure generated by ventilator). Muscle pressure is patient generated, cannot be directly measured, and represents the pressure generated by the patient to expand the thoracic cage and lungs. In contrast, ventilator pressure is the trans-respiratory pressure generated by the ventilator during inspiration. Combinations of these pressures are generated when the patient is breathing with positive-pressure ventilation. In spontaneously breathing patients, the pressure measured at the airway is a mix of the two pressures depending upon the mode of ventilator support utilized. For example, in CPAP all pressure generated will be by the patient's muscles as opposed to pressure support, where the pressure generated will be a mix of the pressure generated by the patient's respiratory muscles and that generated by the ventilator. For example, when respiratory muscles are at complete rest, the muscle pressure is 0; therefore, the ventilator must generate all the pressure necessary to deliver the inspiratory flow and tidal volume. The converse is also true, and there are degrees of support depending upon the amount of force generated by the patient's respiratory muscles. The application of the equation of motion to the generation of gas

Table 8.9 Equation of motion for the respiratory system

Airway opening pressure =	Elastic component +	Resistive component
Pressure =	Elastic pressure +	Resistive pressure
Pressure =	Elastance $\times$ Volume +	Resistance $\times$ Flow
Pressure =	$\frac{\text{Volume}}{\text{Compliance}}$	Resistance $\times$ Flow

flow is the next important step. Therefore, total pressure applied to the respiratory system (PRS) of a ventilated patient is the sum of the pressure generated by the ventilator (measured at the airway) PAO and the pressure generated by the respiratory muscles (P_{mus}) Table 8.9. Therefore,

$$P_{\text{RS}} = P_{\text{Applied}} + P_{\text{mus}}$$

where PRS is the respiratory system pressure, P_{Applied} is the applied pressure by the ventilator, P_{mus} is the pressure developed by the respiratory muscles, is flow, R is airway resistance, is respiratory system compliance, and k is the pressure. P_{Applied} and can be measured by the pressure and flow transducer in the ventilator. Volume is derived mathematically from the integration of the flow waveform.

To generate a volume displacement, the total forces have to overcome elastic and resistive elements of the lung and airway/chest wall represented by and, respectively. Depends upon both the volume insufflated in excess of resting volume and the respiratory system compliance Table 8.10. To generate gas flow, the total forces must overcome the resistive forces of the airway and the endotracheal tube against the driving pressure gradients. At any moment during inspiration, there must be a balance of forces opposing lung and chest wall expansion, measured as the airway pressure (P_{AO}). The opposing pressure can be summarized as the sum of elastic recoil pressure (P_{elastic}), flow-resistive pressure ($P_{\text{resistive}}$), and inertance pressure ($P_{\text{resistance}}$) of the respiratory system:

$$P_{\text{AO}} = P_{\text{elastic}} + P_{\text{resistive}} + P_{\text{inertance}}$$

Inertial forces, which are usually negligible during conventional ventilation, depend upon

bulk convective flow unlike in high-frequency ventilation, where volumes are at the level of dead space. Therefore, for conventional ventilation, the forces exemplified in the equation of motion can be expressed as

$$P_{\text{AO}} = P_{\text{elastic}} + P_{\text{resistive}}$$

If elastic forces are recognized as the product of elastance and volume ($P_{\text{elastic}} = E \times V$) and the resistive forces as the product of flow and resistance ($\text{Resistive} = V \times R$), the formula can be written as

$$P_{\text{AO}} = (\text{Elastance} \times \text{Volume}) + (\text{Resistance} \times \text{Flow})$$

If compliance (the inverse of elastance) is substituted for elastance, the equation of motion becomes

$$P_{\text{AO}} = +\text{Resistance} \times \text{Flow}$$

This relationship is demonstrated in Tables 8.9 and 8.10.

The quotient of volume displacement over compliance of the respiratory system represents the pressure necessary to overcome the elastic forces above the resting lung volume or functional residual capacity (FRC), the quantity of air remaining in the lungs at the end of a spontaneous expiration. Pressure, flow, and volume are all measured relative to their baseline values. Therefore, the pressure necessary to cause inspiration is measured as the change in airway pressure above positive end-expiratory pressure (PEEP). For example, in a patient breathing spontaneously on continuous positive airway pressure (CPAP), the ventilator pressure is 0; the patient must utilize his respiratory muscles to generate all the work of breathing (WOB). The same can be applied to the volume during inspiration or the tidal volume, which is the change in volume above FRC. The pressure necessary to overcome the resistive forces of the respiratory system is the product of the maximum airway resistance (R_{max}) and inspiratory flow. Flow is measured relative to its end-expiratory value, which is usually 0, unless intrinsic PEEP (PEEP_i) is present.

Table 8.10 Manipulation of the equation of motion

Elastic components	Resistive components
$\text{Pressure} = \frac{\text{Volume}}{\text{Compliance}}$	$\text{Pressure} = \text{Resistance} \times \text{Flow}$
or	or
$\text{Volume} = \text{Pressure} \times \text{Compliance}$	$\text{Flow} = \frac{\text{Pressure}}{\text{Resistance}}$
or	or
$\text{Compliance} = \frac{\text{Volume}}{\text{Pressure}}$	$\text{Resistance} = \frac{\text{Pressure}}{\text{Flow}}$

8.1.3.5.3 Functional Characteristics of Mechanical Ventilators

For a discussion of waveform analysis during mechanical ventilation, there must be a differentiation between those variables that are directly controlled by clinicians and those that are indirectly controlled. For example, pressure, volume, and flow are directly controlled variables, as opposed to constants such as resistance and compliance, which are dependent upon the resistive and elastic properties of the respiratory system. For patients who are spontaneously breathing, partially or totally supported on mechanical ventilation, dynamic mechanics may be derived (Iotti et al. 1995a, b).

Each ventilator is a controller of pressure, flow, or volume in the equation of motion (Chatburn and Primiano 2001). The manner, in which each variable is controlled, described as the mode of ventilation, determines how the ventilator delivers the mechanical inflation. In the equation of motion, the forms of any of the variables (pressure, volume, or flow) are expressed as functions of time and can be predetermined. This serves as the theoretical basis for classifying ventilators as pressure, volume, or flow controllers. It is important to recognize that according to the equation of motion, any ventilator can only directly control one variable at a time: pressure, volume, or flow. Therefore, a ventilator is simply a technology that controls the airway pressure waveform, the inspired volume waveform, or the inspiratory flow waveform. Therefore, pressure, volume, and flow are referred to in this context as control variables.

Most clinicians think of ventilators in terms of modes of ventilation. However, the mode

of ventilation is a description of the way a mechanical breath is delivered. The determinants of how a mechanical breath is delivered are summarized not only in the control variables but also in the phase and conditional variables. Conditional variables are determinants of a response to a preset threshold. Control variables are the independent variables. In each phase, a particular variable is measured and is used to start, sustain, and end the phase. The phase variable includes the trigger variable (determines the start of inspiration), limit variable (determines what sustains inspiration), and the cycle variable (determines the end of inspiration).

To understand the interpretation of waveforms, the clinician needs to understand the relationship between the control and phase variables as it relates to the parameters that are either displayed or calculated and shown on the ventilator screen. First, the control variables must be identified for each type of controller, including what the dependent and independent variables are, in order for the clinician to identify the proper waveform (pressure–time, flow–time, or volume–time) representing either the elastic or resistive changes of interest (Tables 8.11 and 8.12).

8.1.3.5.3.1 Control Variables

The control variable must overcome the elastic and resistive forces to allow gas delivery to the patient. The elastic components of the equation of motion related to pressure is

$$\text{Pressure} = \text{Volume} \times \text{Elastance}$$

If a clinician sets pressure as a function of time, volume varies directly with the compliance of the respiratory system. Pressure is the

Table 8.11 Controllers

	Flow controller modes (Constant-flow controller)	Pressure controller modes (Constant pressure controller)	Volume controller modes (Variable-flow controller)
	Volume control, SIMV-VC	Pressure control, PRVC, SIMV-PC	Volume control
Equation	Flow = Pressure/Resistance	Flow = Volume/Compliance Pressure = Resistance × Flow	Flow = Pressure × Compliance
Independent variable	Flow	Pressure	Volume
Dependent variable	Pressure	Volume Flow	Pressure
Limiting variable	Volume	Pressure	Volume
Trigger variables			

Table 8.12 Controller waveform analysis

Flow controller waveform analysis	Pressure controller waveform analysis	Volume controller waveform analysis
Pressure–time waveform is affected by resistance changes	Pressure–time waveform is not affected by resistance and compliance changes	Pressure–time waveform is affected by compliance changes
Flow–time waveform is not affected by compliance and resistance changes	Flow–time waveform is affected by compliance and resistance	Flow–time waveform is not affected by resistance changes
Volume–time waveform is not affected by compliance and resistance changes	Volume–time waveform is affected by compliance and resistance	Volume–time waveform is not affected by compliance and resistance changes

independent variable set by the clinician, and volume is the dependent variable determined by the level of pressure. When the clinician presets the pressure pattern, the ventilator operates as a pressure controller. The volume becomes a function of compliance, so that a decrease in compliance allows less volume to be delivered at the same pressure. During expiration, the elastic and resistive elements of the respiratory system are passive, and expiratory waveforms are not directly affected by the mode of ventilation or controller.

For the resistive components of the equation of motion:

$$\text{Pressure} = \text{Flow} \times \text{Resistance of the total system}$$

The clinician sets pressure as a function of time, allowing flow to vary with resistance. If resistance increases, flow is ultimately limited. Pressure is referred to as the independent variable

and flow as the dependent variable. As previously discussed, expiration is passive and the expiratory profile is not directly affected by the mode of ventilation but rather by compliance and resistance. However, because the respiratory cycle is a set period, any change in the inspiratory time can influence expiratory time and, to a certain point, the expiratory profile.

When a ventilator operates as a constant pressure controller (e.g., in pressure control, pressure-regulated volume control [PRVC] and synchronized intermittent mandatory ventilation–pressure control [SIMV-PC]), pressure is an independent or controlled variable. The set pressure will be delivered and maintained constant throughout inspiration, independent of the resistive or elastic forces of the respiratory system. Although pressure is constant, the delivered tidal volume is a function of compliance and resistance, and the flow varies exponentially with time.

For a waveform illustrated in Fig. 8.33 from a ventilator operating as a pressure controller, volume and flow become the dependent variables, and their patterns will depend upon compliance and resistance of the respiratory system.

Characteristics of the flow–time waveform shows a rapid increase to peak inspiratory flow (PIF) with flow decelerating through the inspiratory time with exponential decay to baseline. During expiration there is a rapid decrease to peak expiratory flow (PEF) with exponential decay to baseline with normal end-expiratory flow being zero. Increased airway resistance is evident when flow persists at the end of expiration with a slow and linear expiratory decay to baseline.

With this waveform evidence of patient–ventilator interactions is identified. Secretions in the airways or water in the connecting tubing can cause evidence of a sawtooth (noisy) pattern in the inspiratory and/or expiratory profile. Also use of respiratory muscles during expiration can change both the duration and pattern of expiratory flow profile.

In a pressure–time waveform during a constant pressure mode, there is a rapid increase to PIP with pressure being constant during the inspiratory time. During the expiratory time flow is exponential to baseline. Elastic and resistive components are not reflected in the inspiratory profile, but an increase in expiratory resistance is associated with a linear decay to baseline.

Patient–ventilator interactions are evident by fluctuations in triggering efforts suggesting asynchrony between the patient and the ventilator. Evidence of plateau pressure not reaching set pressure may be evidence of a leak.

Flow and resistance are only associated with the resistive components of the equation of motion. The elastic components refer to volume and compliance. The resistive components of the equation of motion are

$$\text{PIP} - P_{\text{plateau}} / \text{Peak inspiratory flow}$$

$$\begin{aligned} \text{Flow} &= \text{Pressure} / \text{Resistance or} \\ \text{Pressure} &= \text{Resistance} \times \text{Flow} \end{aligned}$$

Therefore, if the clinician sets flow as a function of time, pressure then varies with resistance. Flow is the independent variable, and pressure is the dependent variable. When a flow pattern is preset, the ventilator operates as a flow controller, the pressure is a function of resistance, and the inspiratory–pressure–time waveform varies linearly with time. Volume increases linearly with time but does not have a direct relationship to flow. Volume does have an indirect relationship to flow because volume is the integral of flow and flow is derivative of volume.

Expiration is passive, and the expiratory profile is not directly affected by mode of ventilation but rather by compliance and resistance, although the set inspiratory time can influence the expiratory time and to a certain point the respiratory profile.

When a ventilator operates as a constant-flow controller (e.g., SIMV-VC), flow is the independent variable. Regardless of what the resistive or elastic forces of the respiratory system are, the set flow will be delivered and maintained constant throughout inspiration. Pressure and tidal volume will vary with time but are functions of compliance and resistance.

Figure 8.34 illustrates the waveform from a ventilator operating as a flow controller. Flow is the independent variable (controlled variable); pressure and volume are dependent variables. With a preset flow pattern, pressure and volume vary linearly with time and are affected by compliance and resistance.

In the pressure–time waveform, during inspiration there is an exponential increase in the first portion with a linear increase to PIP with an exponential decrease from PIP to P_{pause} . During expiration there is an exponential decay to baseline or level of PEEP. Dynamic characteristics of elastic and resistive components are reflected in the inspiratory profile. An increase in expiratory resistance is associated with a linear decay to baseline. Evidence of fluctuations in PIP and triggering effort reflects asynchrony.

If one examines the flow–time waveform for a constant-flow modality in Fig. 8.34, different characteristics can be identified in each phase of ventilation. In the inspiratory phase, there is a rapid rise to peak inspiratory flow (PIF), with

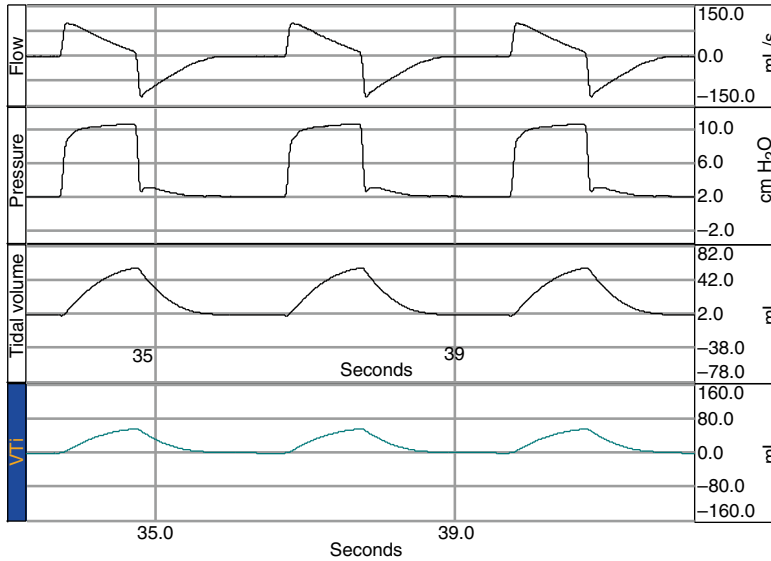


Fig. 8.34 Flow–time, pressure–time, and volume–time waveforms during a constant pressure mode under normal conditions. Flow characteristics are similar to a constant-flow mode in the flow–time waveform. The pressure–time waveform demonstrates a rapid increase to peak inspiratory pressure and exponential decay to baseline. It is important to note that elastic and resistive components are not reflected in the inspiratory profile. An increase in expiratory resistance is associated with a linear decay

to baseline. Also unreached pressure plateau is associated with evidence of leakage at the airway or ventilator system. For the volume–time waveform, there is an exponential rise to inspired tidal volume and decay to baseline during expiration. Elastic and resistive components are reflected in the inspiratory and expiratory profiles. A sudden return to baseline at the start of inspiration is associated with evidence of leakage

flow being constant during inspiration. No flow occurs during the pause time. During expiration, there is a rapid decrease to peak expiratory flow (PEF) with an exponential decay to baseline. End-expiratory flow should be zero; flow present at the end of expiration is evidence of increased resistance. This is further evident with the presence of a slow linear expiratory decay to baseline.

Like the pressure–time waveform, secretions in the airways or water in the connecting tubing can cause turbulent flow, resulting in a sawtooth pattern in the inspiratory and/or expiratory profile. Also, the use of respiratory muscles during expiration can change both the duration and pattern of the expiratory flow profile.

Modern ventilators operate as either flow or pressure controllers. As a flow controller, the most common pattern is constant flow,

also referred to as a square wave flow pattern (Fig. 8.33 square waveform). As a pressure controller, the only pressure pattern is a constant pressure, also referred to as square wave pressure pattern (Fig. 8.34).

From the equation of motion, one can infer that with ventilator operating as a constant-flow controller, the pressure and volume are linear functions of time. Different ventilators have the possibility of delivering various flow patterns.

Alternative flow patterns, beyond constant and exponentially decelerating flow, need to be controlled by a microprocessor that sequentially adjusts flow using an algorithm to create the decelerating ramp, ascending ramp, and sinusoidal flow patterns. These flow patterns are used in various volume-targeted modes. The decelerating rate controlled by the algorithm

produces a linear deceleration that does not reflect elastic and resistive elements of the respiratory system. A linear deceleration is often associated with flow-starvation asynchrony because flow is not a dependent variable in such a mode. Not all ventilators can produce these flow patterns. The exponentially decreasing flow pattern is available with a pressure-control or dual-control modality.

Theoretically, it has been proposed that a decelerating flow favors better gas exchange and improves distribution of ventilation among lung units with heterogeneous time constants. However, neither animal nor clinical studies have documented this advantage.

Volume is associated with the elastic component of the equation. The resistive components refer to resistance and flow. The elastic components can be rearranged to indicate how volume is determined.

If the clinician sets volume as a function of time, pressure then varies with compliance. Volume is an independent variable and pressure is a dependent variable. Expiration is passive, and the expiratory profile is not directly affected by the mode of ventilation but rather the compliance and resistance, although the set inspiratory time can influence the expiratory time and, to a certain extent, the expiratory profile.

When a ventilator sets a volume pattern, it operates as volume controller. However, to truly be a volume controller, the ventilator must measure volume directly to set the volume pattern. Most ventilators do not directly measure volume; rather, they calculate volume over a period of time. Most ventilators use volume as a limit variable; that is, inspiration stops when the preselected volume is reached. When inspiration stops at the preset volume, the ventilator is referred to as being volume cycled but is actually a flow controller. Additionally, true volume cycling cannot occur with an uncuffed endotracheal tube, as there will be a variable degree of leak around the tube, especially during inspiration.

The relationship between the gas delivery and the resistive and elastic elements of the patient and ventilator system is important for under-

standing the delivery of a positive-pressure breath to a patient.

8.1.3.5.3.2 Phase Variables

Phase variables control the ventilator between the beginning of one breath and the initial phase of the next breath. Phase variables are important determinants of how a ventilator initiates, sustains, and ends inspiration and what it does between cycles. A specific variable is measured and used to initiate, sustain, and end each phase. The phase variable includes the trigger, which determines the initiation of inspiration; a limit variable, which determines what sustains inspiration; and a cycle variable, which determines the termination of inspiration. Changes in the phase variable can affect and be reflected by forces and influence the patient's work of breathing. Work of breathing is discussed elsewhere; we will focus on the effects in the phase variables displayed in ventilator waveforms that reflect patient-ventilator asynchrony.

8.1.3.5.3.3 Limit Variable

The limit variable sustains inspiration. Inspiratory time is defined as the interval from the beginning of inspiratory flow to the beginning of expiratory flow. During inspiration, pressure, volume, and flow increase above their end-expiratory values. If one or more of these variables increase no higher than the preset value, this is referred to as the limit variable. However, it is important to recognize that the limit variable determines the factors that sustain inspiration but differs from the cycle variable, which determines the end of inspiration. Therefore, a limit value does not terminate inspiration but increases it to a preset value. A limit variable that is set below the level desired by the patient can lead to patient-ventilator asynchrony and will be discussed below.

8.1.3.5.3.4 Cycle Variables

The cycle variable terminates inspiration once a preset value is obtained. The cycle variable differs for various modes of ventilation. In pressure support, the termination of the breath is

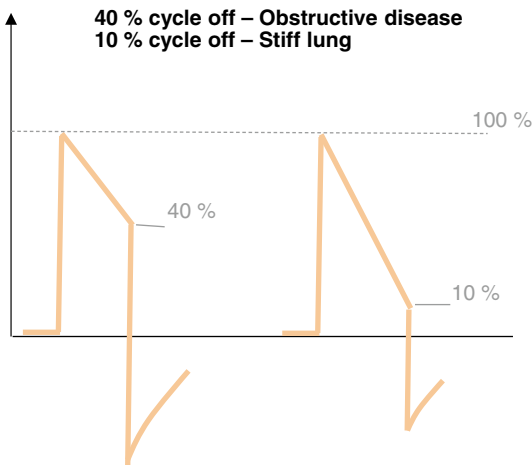


Fig. 8.35 The cycling-off parameter. The cycling-off parameter is based on a percentage of peak flow. Thus, at 10 % inspiratory time is prolonged and at 40 % it is shortened. If the cycle parameter is set at 40 %, the patient spends a greater time during expiration which would be advantageous in a patient with obstructive disease. If the cycling-off parameter is set at 10 %, then there is a longer inspiratory phase which would be advantageous in a patient with decreased pulmonary compliance or stiff lungs

traditionally triggered by the absolute level of flow or by decay to a fixed percentage of peak inspiratory flow. Until recently, clinicians had little control over inspiratory time because it relates to the patient's pathology. For example, for a patient with increased airway resistance and dynamic hyperinflation, it may be desirable to shorten the inspiratory time and use a prolonged expiratory phase. By changing the cycle variable, as illustrated in Fig. 8.35, the patient's inspiratory phase can be shortened, allowing a longer expiratory phase. The opposite is also true for patients with decreased pulmonary compliance, where the clinician might want to prolong the inspiratory phase.

8.1.3.5.4 Monitoring Increased Airway Resistance

During mechanical ventilation the delivery of a positive-pressure breath requires overcoming both resistive and elastic forces. Increased airway resistance causes the resting volume at the end of exhalation to be increased because of lower expiratory flows and short expiratory times. To understand resistance during positive-pressure mechanical ventilation, airflow during both inspi-

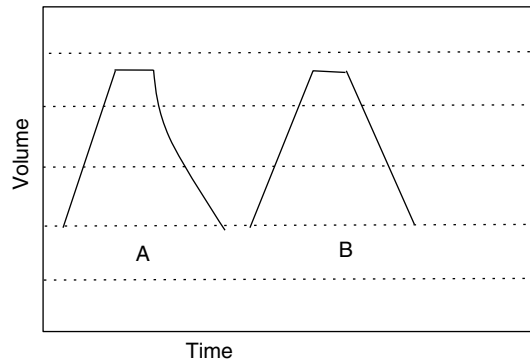


Fig. 8.36 A volume-time waveform during a constant-flow mode. A illustrates increased resistance and B normal resistance. The effects of increased resistance can be seen in A with a slower exponential decay to baseline

ration and expiration (as a measure of the flow-resistive elements of the respiratory system) needs to be considered. Resistance can be expressed as

$$\text{Pressure/Flow}$$

Flow, tidal volume, and the dimensions of the gas delivery system, including the patient's endotracheal tube, affect airway resistance. In pediatric patients, resistance to gas flow is primarily caused by the endotracheal tube. In the neonate, small diameter airways are also contributory. When delivering a positive-pressure breath with a set tidal volume and flow, the resistance created by the endotracheal tube is directly related to both the diameter and length of the tube. In examining resistance during positive-pressure mechanical ventilation, the type of controller delivering the mechanical breath must be considered. For example, if a mechanical breath operates as a pressure controller [e.g., pressure control (PC), pressure-regulated volume control (PRVC), or synchronized intermittent mandatory ventilation (SIMV)-PC], the following relationship from the equation of motion occurs:

$$\text{Flow} = \text{Pressure/Resistance}$$

The dependent variables are volume and flow and the independent variable is pressure (Tables 8.11 and 8.12). The resistive elements of both within the respiratory system and breathing circuit are visualized in flow-time and volume-time waveforms (Figs. 8.36, 8.37, 8.38,

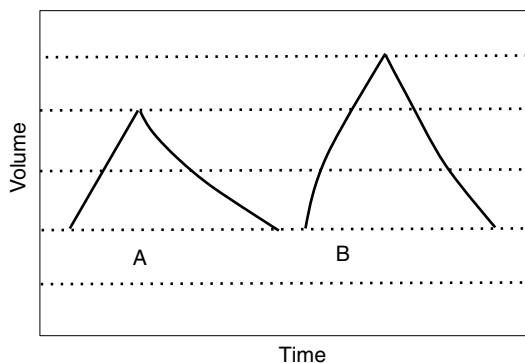


Fig. 8.37 A volume–time waveform during a constant pressure mode. *A* illustrates increased resistance and *B* normal resistance. The effects of increased resistance can be seen in *A* during linear increase vs exponential increase to inspired tidal volume. Also in expiration with a linear decay vs exponential decay seen in normal resistance

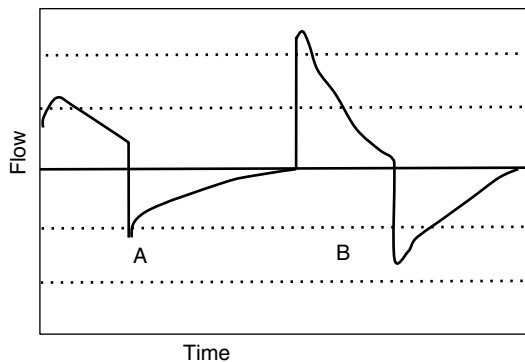


Fig. 8.38 A flow–time waveform during a constant pressure mode. Tracing *A* illustrates increased resistance. During the inspiratory phase PIF is decreased with a linear and slower decay to baseline. Inspiration stops before baseline. During expiration PEF is decreased and there is a linear decay to baseline. Tracing *B* illustrates normal resistance with higher PIF with an exponential decay and faster decay to baseline. During expiration there is a higher PEF and an exponential decay to baseline

and 8.39). Because pressure is the independent variable, it is held constant during inspiration, and a pressure–time waveform does not illustrate the effects of resistance. In contrast, because the rate of decay of flow is a function of resistance, a flow–time waveform illustrates resistance. For ventilator modes that use a flow controller (e.g., volume control, SIMV-VC), $\text{Flow} = \text{Pressure} / \text{Resistance}$, the independent variable is flow and the dependent variable is pressure. When

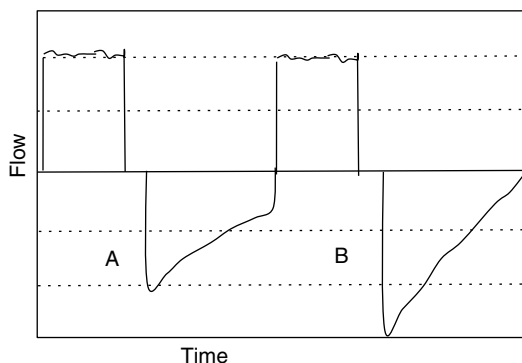


Fig. 8.39 A flow–time waveform during a constant-flow mode. Tracing *A* illustrates increased resistance. During the inspiratory phase tracing *A* is similar to tracing *B*. During expiration PEF is lower with a linear and slower decay to baseline as compared to tracing *B*. Nonzero flow at the end of expiration is illustrative of auto-PEEP. Tracing *B* illustrates normal resistance with inspiration similar to tracing *A*. During the expiratory phase PEF is higher with decay being exponential and faster to baseline. There is zero flow at end of expiration

a ventilator operates in a constant-flow mode, the resistive elements of the respiratory system and breathing circuit can be visualized and calculated with a pressure–time waveform, which begins with an exponential rise to a first step, followed by a linear rise to peak inspiratory pressure (PIP).

During the initial portion of inspiration, the first step is a function of flow and resistance, with the size of the step directly related to the degree of resistance. The second portion of the waveform is a linear increase to PIP and is a function of flow being constant throughout inspiration, and it represents the elastic properties of the respiratory system.

As PIP is reached, a pause time or plateau is maintained while pressure inside the airways and the breathing circuit equilibrates at plateau pressure (P_{plateau}). Flow then stops while pressure equilibrates.

Figure 8.38 is a pressure–time waveform from constant-flow ventilation and illustrates various elements related to resistive and elastic properties of the respiratory system.

Inspiratory resistance (R_i) is the difference between the PIP and the P_{plateau} divided by peak

inspiratory flow at PIP, as expressed by the following equation:

$$\text{PIP} - P_{\text{plateau}} / \text{Peak inspiratory flow}$$

Expiratory resistance is the difference between P_{plateau} and total PEEP over flow value at the onset of exhalation, as expected from the following equation:

$$P_{\text{plateau}} - \text{total PEEP} / \text{Flow (at onset of expiration)}$$

Figure 8.39 demonstrates flow–time and pressure–time waveforms for constant-flow ventilation and illustrates various landmarks for resistance calculations.

8.1.3.5.4.1 Patients with Increased Airway Resistance

Airway resistance (R_{AW}) is the sum of periphery airway resistance peripheral airway resistance (peripheral intrathoracic airways <2 mm diameter R_{awp}), the central airway resistance, and extrathoracic airway resistance. In intubated patients receiving mechanical ventilation, the patient's airway resistance has to take into account the endotracheal tube and resistive components of the circuit and triggering system. Obstructed airway disease may result from an obstruction at an extrathoracic or intrathoracic site. For diagnostic purposes, flow–volume loops can be diagnostic and help to guide therapeutic interventions.

Extrathoracic obstruction involving the airway primarily limits airflow from entering the lungs on inspiration. Non-intubated patients will present with stridor, as seen in croup, laryngomalacia, tracheomalacia, and epiglottitis. In contrast, variable intrathoracic airway obstruction primarily limits gas from exiting the lung during exhalation. Patients breathing through narrowed airways impose an additional load on the respiratory muscles that is exacerbated with increased airway resistance.

In patients with increased airway resistance, the resting volume at the end of exhalation is increased because of lower expiratory flows and short expiratory times. As a result, a positive recoil pressure (PEEP_i) is created at the end of expiration, and a new resting state is established. This state of air trapping or dynamic hyperinflation is common in patients with obstructive disease such as asthma or bronchopulmonary dysplasia. Initially in these patients, hyperinflation

tends to keep airways open, reduces airway resistance, increases elastic recoil, and tends to improve expiratory flow. However, hyperinflation has several deleterious effects. The positive pressure within regions of hyperinflated lung increases the mean intrathoracic pressure and causes the inspiratory muscles to operate at a volume higher than the resting volume. Respiratory muscle function becomes impaired because dynamic hyperinflation places respiratory muscles at a considerable mechanical disadvantage. PEEP_i imposes a substantial inspiratory threshold, as flow is limited because of negative intrapleural pressure equal to the level of PEEP_i that has to be generated before inspiratory flow can begin within the alveoli. This threshold load imposed by PEEP_i may interfere with ventilator triggering requiring the patient to overcome the imposed PEEP_i before the trigger to threshold is reached. Moreover, the ventilation–perfusion relationship can be impaired because the hyperinflated lung may compress adjacent areas of the normally inflated lung. PEEP_i also decreases cardiac output by increasing intrathoracic pressure, thereby reducing venous return, and predisposes the patient to barotrauma by causing dynamic hyperinflation. Therefore, the mainstay of therapy in patients with obstructive lung disease requiring mechanical ventilation is the reduction of dynamic hyperinflation.

When a ventilator operates in a constant pressure mode, the resistive elements of the respiratory system/breathing circuit can be visualized with the flow–time and volume–time waveforms. The inspiratory part of the pressure–time waveform does not offer any indication of resistance, since pressure is constant throughout inspiration. However, the flow–time waveform will reflect the resistive element of the respiratory system since the rate of decay of flow is a function of resistance. For measuring resistance, the expiratory flow–time waveform aids the clinician in detecting the presence of dynamic hyperinflation or detecting the presence of dynamic hyperinflation or intrinsic PEEP. Expiratory flow shows air trapping when it fails to return to zero. When the expiratory time is not long enough to allow exhalation of all the tidal volume, auto-PEEP is generated. In a flow–volume loop, air trapping is characterized by a truncated expiratory phase that does not return to baseline (Blanch et al. 2005; Dhand 2005).

8.1.3.5.4.2 Measuring Resistance in Constant-Flow Mode of Ventilation

Traditionally, resistance has been measured by the interrupter technique. Flow is interrupted at the end of inspiration while pressure is held constant during a period of time (pause). The interrupter technique is only valid when the ventilator operates in a constant-flow mode.

When a ventilator operates in a constant-flow mode, the resistive elements of the respiratory/breathing circuit can be visualized and calculated with the pressure–time waveform. The pressure–time waveform begins with an exponential rise to a first step, followed by a linear rise to peak inspiratory pressure (PIP).

The first step is a function of flow and resistance during the initial portion of inspiration. The higher the step, the larger the resistance. The second portion of the waveform is a linear increase to PIP and is a function of flow being constant throughout inspiration. This second portion represents the elastic properties of the respiratory system. As seen in Fig. 8.40, PIP is reached, a pause time or plateau is maintained, while pressure inside the airways and the breathing circuit equilibrates at plateau pressure (P_{plateau}). Flow then stops while pressure equilibrates.

Inspiratory resistance is the difference between PIP and P_{plateau} , as expressed by the following equation:

$$\text{PIP} - P_{\text{plateau}}$$

Expiratory resistance is the difference between P_{plateau} and total PEEP divided by flow value at the onset of exhalation, as expressed by the following equation:

$$P_{\text{plateau}} - \text{total PEEP} / \text{Flow (at onset of expiration)}$$

Specific measuring conditions must be met for a valid inspiratory and expiratory resistance value: (1) passive tidal volume (inspiration and expiration), (2) constant flow over a fixed inspiratory time, (3) T_i (for inspiratory resistance only), and (4) P_{plateau} must have an end-inspiratory pause of at least 1 s with a stable pressure within 0.5 cm H₂O over two readings at least 10 ms apart.

The pressure–time waveform under a constant-flow mode with a pause time has been previously

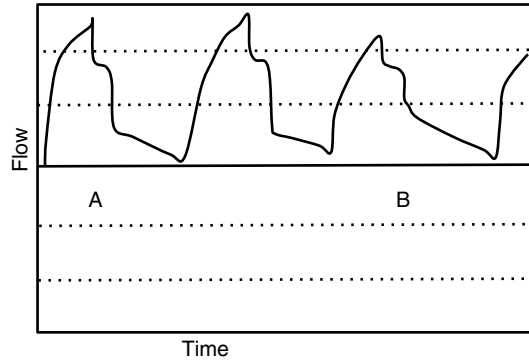


Fig. 8.40 A pressure–time waveform during a constant-flow mode of ventilation. Tracing A illustrates increased resistance. During the inspiratory phase there is a linear increase to the first portion and an exponential increase to PIP. The difference between PIP and P_{plateau} is increased. During expiration the exponential decay is slower and almost linear with baseline reaching the set PEEP

described. The pause time can be analyzed in detail and brings subdivisions in the resistance concept. The pressure decrease from PIP to the end of P_{plateau} can be magnified. Two segments of resistance can be calculated: the maximum resistance index (R_{max}) and the minimum resistance index (R_{min}).

Figure 8.41 shows flow–time and pressure–time waveforms from constant-flow ventilation and illustrates various landmarks for resistance calculations. In this figure, PIP is the peak inspiratory pressure and represents the peak dynamic pressure. P_z is the airway pressure when flow stops (zero flow) during pause time. The exact location of P_z is not yet clearly identified. P_{plateau} is the end-inspiratory pause pressure (representing the static airway pressure) and is often referred to as a close estimate of the alveolar pressure. The slow decay after the drop from PIP to P_z depends on the viscoelastic properties of the system and on the pendulum-like movement of the air (pendelluft) (Rossi et al. 1985a, b; Milic-Emili and Polysongsang 1986; D’Angelo et al. 1989; Bates et al. 1988; Stenqvist 2003).

In contrast, R_{max} is the difference between PIP and P_{plateau} at peak inspiratory flow. R_{max} represents the resistance caused by the endotracheal tube, the breathing circuit, pulmonary tissues, and the thoracic cavity at maximum lung volume.

Fig. 8.41 Flow–time and pressure–time waveforms during a constant-flow mode

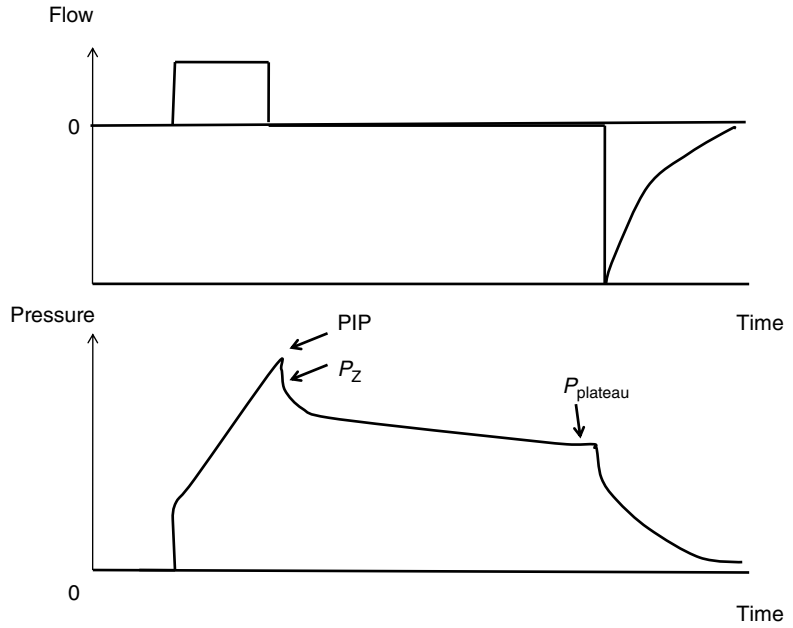


Table 8.13 Values of $R_{\max}$ and $R_{\min}$ in adults

Adults	$R_{\max}$ (cm H ₂ O/L/s)	$R_{\min}$ (cm H ₂ O/L/s)
Normal	7	2.5
ARDS	12–15	8.0
COPD	26	15
Pulmonary edema	7–18	4–12

$R_{\max}$ is calculated using the following equation:

$$\text{PIP} - P_{\text{plateau}} \text{ (at peak inspiratory flow)}$$

$R_{\max}$ constitutes the overall resistance of the respiratory system/breathing circuit traditionally calculated during mechanical ventilation. Table 8.13 illustrates various values of $R_{\max}$ and $R_{\min}$ for adults under specific conditions. Table 8.14 illustrates various $R_{\max}$ clinical values for infants under specific conditions.

Minimum resistance index ($R_{\min}$) is the difference between PIP and P_z at peak inspiratory flow. P_z is the pressure value when the expiratory valve closes and flow stops. $R_{\min}$ describes a specific component of the $R_{\max}$ and reflects only the resistance of the airways. $R_{\min}$ is calculated by the following equation:

$$R_{\min} = \text{PIP} - P_z \text{ (at peak inspiratory flow)}$$

Table 8.14 Values of $R_{\max}$ for intubated and extubated infants

	$R_{\max}$ (cm H ₂ O/L/s)	
Infants	Intubated	Extubated
3.0-mm ID	128	75
3.5-mm ID	73	37
Tube size not specified	50–150	20–30

The calculation of $R_{\min}$ itself presents certain difficulties as to precisely identifying the location of P_z . P_z has value greater than the P_{plateau} . The difference between P_z and P_{plateau} represents the gas distribution of alveolar regions with different time constants. However, the zones are ventilated even though the flow in larger airways seems to have stopped.

This phenomenon is often referred to as the pendelluft, the German word for pendulum of air. The larger the difference between $R_{\max}$ and $R_{\min}$, the larger the zones of discrepancies. In ARDS, the differences between P_z and P_{plateau} generally differ by 10–20 %.

8.1.3.5.5 Monitoring Compliance in Mechanical Ventilation

Compliance expresses the elastic components as a volume change divided by a pressure change and can be expressed by the following equation:

$$\text{Compliance} = \Delta V / \Delta P$$

Respiratory system compliance (C_{RS}) is related to lung compliance (C_{pulm}) and chest wall compliance (C_{CW}) by the following equation:

$$C_{RS} = \Delta \text{Volume} / \Delta (P_{AO} \text{ airway opening} - P_{bs} \text{ pressure at the body surface or atmospheric pressure})$$

C_{RS} may be used to evaluate and modify various therapeutic interventions such as tidal volume and PEEP titration, skeletal muscle relaxation, and patient positioning. In the preterm newborn, the chest wall is usually more compliant than the lung.

Chest wall compliance (CCW) is not commonly calculated during mechanical ventilation; it requires an estimate of intrapleural pressure changes not requiring an indwelling esophageal catheter.

Chest wall compliance describes the changes in tidal volume relative to the pleural pressure, reflected by the esophageal pressure (P_{eso}), and is expressed by the following equation:

$$\text{Chest wall compliance} = \Delta V / \Delta P$$

Chest wall compliance can usually be estimated at 4 % of the vital capacity per cm H_2O . Normal value for chest wall compliance is approximately 200 mL/cm H_2O .

Lung compliance is also not commonly calculated in patients on mechanical ventilator support because of the same limitations that apply to the calculation of chest wall compliance. Lung compliance describes a change in tidal volume relative to alveolar pressure reflected as plateau pressure and esophageal pressure under quasi-static conditions. This is reflected in the following equation:

$$C = \Delta V / \Delta P$$

Total static compliance (during a no-flow activity at the end of inspiration and expiration) and total dynamic characteristics (during active inspiration) are two conditions when the volume–pressure relationship is most often monitored in mechanical ventilation.

In order to measure static compliance during mechanical ventilation, specific conditions must be met including that tidal volume must be passive (both inspiration and expiration), compressible volume of the ventilator circuit must be corrected,

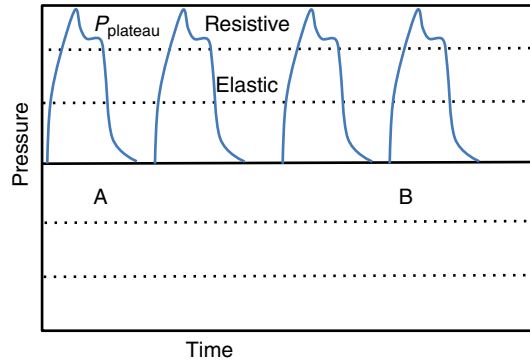


Fig. 8.42 A pressure–time waveform during a constant-flow mode of ventilation illustrating areas related to resistive and elastic properties of the respiratory system

and plateau must have an end-inspiratory pause of at least 1 s with a stable pressure within 0.5 cm H_2O over two readings at least 10 ms apart.

Total static compliance is reflective of changes in lung elasticity and describes the delivery of tidal volume relative to the airway pressure under static conditions and is expressed as

$$C_{stat} = \Delta V / (P_{plat} - PEEP)$$

The status of compliance at the bedside can be observed with flow–time and pressure–time waveforms and pressure–volume loops. Pressure–volume loops will be discussed in another section. It is important to note that compliance values are affected by a number of parameters including patient size, state of relaxation, lung volume, and flow, thus necessitating caution when applying actual values of compliance. Thus, trended values offer more accurate clinical guidance than a specific value at any time point. Also specific waveforms illustrated below can be reflective of changes in dynamic characteristics (Suter et al. 1978) which represents the tidal volume relative to the peak airway pressure.

Figure 8.42 is a pressure–time waveform from constant-flow ventilation and illustrates areas related to resistive and elastic properties of the respiratory system.

Figure 8.43 demonstrates a flow–time waveform from constant-flow ventilation with decreased and normal compliance. Decreased compliance can be detected by examining the slope of the second portion of expiratory flow, which is sharper.

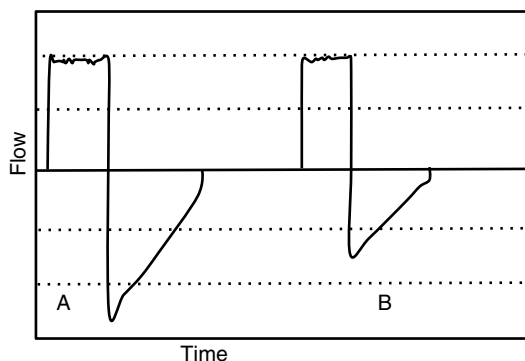


Fig. 8.43 A flow–time waveform during a constant-flow mode of ventilation. Tracing A illustrates decreased compliance. The inspiratory phase is similar to tracing B but the expiratory phase demonstrates a linear and faster decay to baseline

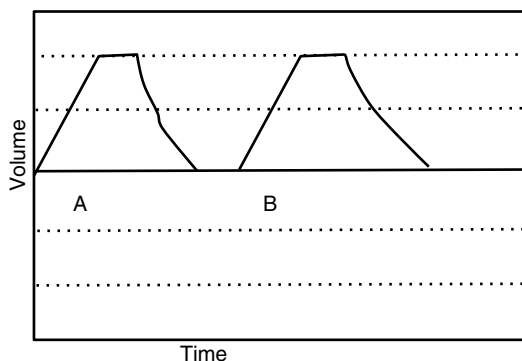


Fig. 8.45 A volume–time waveform utilizing a constant-flow mode. Tracing A illustrates decreased compliance. The inspiratory phase is similar between the two tracings. The expiratory phase for tracing A has a faster exponential decay to baseline than tracing B

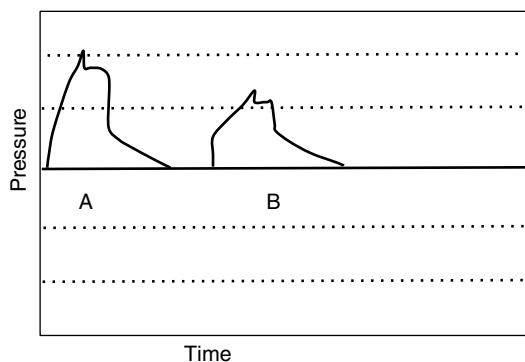


Fig. 8.44 A pressure–time waveform from a constant-flow mode of ventilation with decreased and normal compliance. Tracing A illustrates decreased compliance. During inspiration the first portion is similar to normal compliance tracing but the slope of the second portion is steeper. In this example PIP minus P_{pause} is identical to tracing B. During the expiratory phase there is a steeper exponential decay to baseline

Figure 8.44 demonstrates a pressure–time waveform utilizing constant flow; decreased compliance is detected by examining the second portion of the expiratory waveform where the slope is steeper.

Figure 8.45 demonstrates a volume–time waveform utilizing a pressure mode of ventilation; decreased compliance is detected by examining the peak of the waveform. With decreased compliance the peak has a plateau because flow reaches zero before the elapsed inspiratory time.

Figure 8.46 demonstrates a flow–time waveform utilizing pressure ventilation; decreased compliance is detected by examining both the inspiratory and expiratory waveforms. With

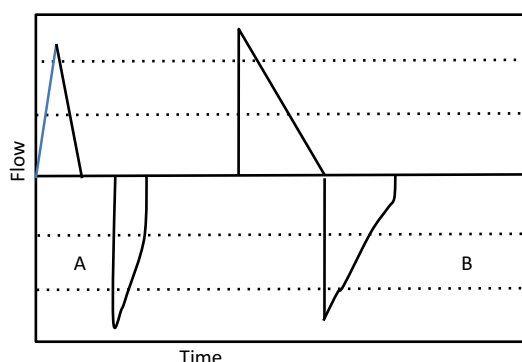


Fig. 8.46 A flow–time waveform during a constant pressure mode. Tracing A illustrates decreased compliance. During inspiration there is a rapid decay to baseline before end of set inspiratory time. Tracing A has lower tidal volume than in tracing B. During the expiratory phase the slope is steeper than in the second portion of tracing B

decreased compliance, there is a rapid decay to baseline before the set inspiratory time has elapsed; subsequently, tidal volume is lower than seen in a normal tracing despite the same peak pressure. During expiration with decreased compliance, the slope is steeper.

During constant-flow ventilation (volume control ventilation) in a completely relaxed patient, the time course of P_{aw} depends linearly on the total respiratory system compliance. The mathematical analysis of the shape of the dynamic pressure–time profile or visualization of the shape of the P_{aw} curve allows detection of hyperinflation or lung recruitment by changing morphology of the curve turning from concave to convex, respectively (Milic-Emili

Table 8.15 Flow–time waveform from a constant-flow mode of ventilation

Characteristics	Potential interventions
Dynamic hyperinflation	Adjusting respiratory rate is indicated Adjusting inspiratory time if indicated Check for auto-PEEP
Auto-PEEP	Adjusting respiratory rate if indicated Adjusting external PEEP if indicated Decrease airway resistance by use of bronchodilator
Dynamic airway compression	Bronchodilator therapy if indicated Suctioning if indicated
Increased inspiratory resistance	Adjusting inspiratory time if indicated Checking mode of ventilation if indicated
Patient–ventilator asynchrony	Changing mode of ventilation if indicated Reviewing patient’s level of sedation Reviewing triggering modality if indicated
Leakage	Faulty breathing circuit connections Anatomical leakage

et al. 1987; Ranieri et al. 1994). Ranieri et al. (Ranieri et al. 2000; Grasso et al. 2004) described these changes mathematically as the stress index in an animal study predicting lung recruitment.

8.1.3.5.6 Detection of Air Leaks

The presence of an air leak may affect the ability to interpret ventilator waveforms or lead to malfunction of the ventilator by causing auto-triggering, inability to maintain PEEP, hypoventilation, or lung de-recruitment from loss of inspired volume. The source of the leak could be caused by an endotracheal tube leak, cuff failure, or loose connection in the ventilator circuit or humidification system. A leak can be detected by comparing the difference between the displayed inspired and expired tidal volume, failure of closure of flow–volume and/or pressure–volume loop, or a volume waveform that fails to return to zero baseline.

8.1.3.5.7 Clinical Interventions

The ultimate goal of utilizing mechanical ventilation waveforms is both to guide the clinician in identifying possible changes in the patient’s respiratory status and to guide interventions. As discussed previously, the detection of changes in the patient’s clinical condition such as increased resistance or decreased compliance

requires an understanding of the mode of ventilation and the displayed waveform. Table 8.15 illustrates potential clinical characteristics that can be identified from a flow–time waveform during a constant-flow mode of ventilation.

Conclusion

This chapter illustrates the basic principles of respiratory mechanics and how they pertain to the interpretation of pulmonary waveforms. Use of pressure, flow, and volume waveforms is a useful – and necessary – adjunct to mechanical ventilation and provides the clinician with important information regarding pulmonary pathophysiology and the patient’s response to and interaction with mechanical ventilation.

Future Perspectives

Over the past 10 years, mechanical ventilators have been developed that offer the clinician increasing information regarding the patient’s physiological status and the effects of clinical interventions. The key to future development will be to further integrate information generated from the ventilator and patient into computerized control algorithms to allow for rapid changes in ventilator support to meet the patient’s clinical needs. Future advances will include integration of currently unused physiological signals and power of the processing by the computer in the ventilator.

Essentials to Remember

- In waveform analysis during mechanical ventilation, there must be a differentiation between those variables that are directly controlled by clinicians and those that are indirectly controlled. For example, pressure, volume, and flow are directly controlled variables, as opposed to constants such as resistance and compliance, which are dependent upon the resistive and elastic properties of the respiratory system.
- During inspiration, flow and pressure patterns are directly related to the forces generated by the ventilator.

- During expiration, flow, pressure, and volume patterns cannot be directly manipulated by the clinician, except for determining the duration of each cycle when using a control mode.
- A ventilator is simply a technology that controls the airway pressure waveform, the inspired volume waveform, or the inspiratory flow waveform.
- To understand the interpretation of waveforms, the clinician needs to understand the relationship between the control and phase variables as it relates to the parameters that are either displayed or calculated and shown on the ventilator screen.

8.2 Nonconventional Ventilation Modes

8.2.1 High-Frequency Ventilators

Martin Keszler, Jane J. Pillow,
and Sherry E. Courtney

Educational Aims

- Describe the principles of function of clinically available high-frequency ventilators.
- Review basic principles of gas exchange and how gas exchange is affected by the specific characteristics of the various devices.
- Describe the limitations of available devices and possible future developments.

High-frequency ventilation (HFV) nominally refers to those ventilator modalities utilizing breathing rates greater than 150 inflation/min and tidal volumes near or even below the anatomical dead-space volume. There are three main types of high-frequency ventilation in clinical use including high-frequency oscillatory ventilation

(HFOV), high-frequency jet ventilation (HFJV), and high-frequency flow interruption (HFFI). In this chapter, we will define the different forms of high-frequency ventilators highlighting similarities and differences in operation and functionality that influence optimal ventilator strategy to be used with each modality. A thorough understanding of these differences and the operation and limitations of these ventilators is necessary to interpret differences in clinical trials and to avoid causing injury to the patient when changing between HFO ventilators or ventilatory modalities. New and improved ventilators are likely to emerge with further technological advances which may overcome current limitations of contemporary high-frequency ventilation devices.

8.2.1.1 High-Frequency Oscillatory Ventilators

8.2.1.1.1 Principles of Functioning and Gas Exchange

8.2.1.1.1.1 Classification of HFO Ventilators

High-frequency oscillation (HFO) is the most well-known and used form of high-frequency ventilation. While some clinical reports of HFOV use stem from the 1970s, more widespread utilization of HFOV as a neonatal ventilator modality stems from the first large randomized controlled trial in the mid-1980s. Since then, HFOV has been subjected to extensive *in vitro* and *in vivo* clinical evaluation.

In general, HFO ventilators are designed to provide ventilation through an endotracheal tube (ETT). They have a clearly defined active inspiratory and expiratory phase that generates biphasic pressure waveforms and diverts small volume packages of fresh bias flow to the patient at frequencies equal to or greater than 3 Hz (typically 6–15 Hz in newborn infants, 4–10 in pediatric patients). Despite this simple description, there has been a long-standing controversy about how to classify certain HFO devices. This controversy stems in part from continued confusion regarding the definition of what exactly constitutes “oscillatory ventilation.” There is general agreement that to qualify as an oscillator, a device has to generate a waveform that has both positive and negative pressure deflection. The biphasic

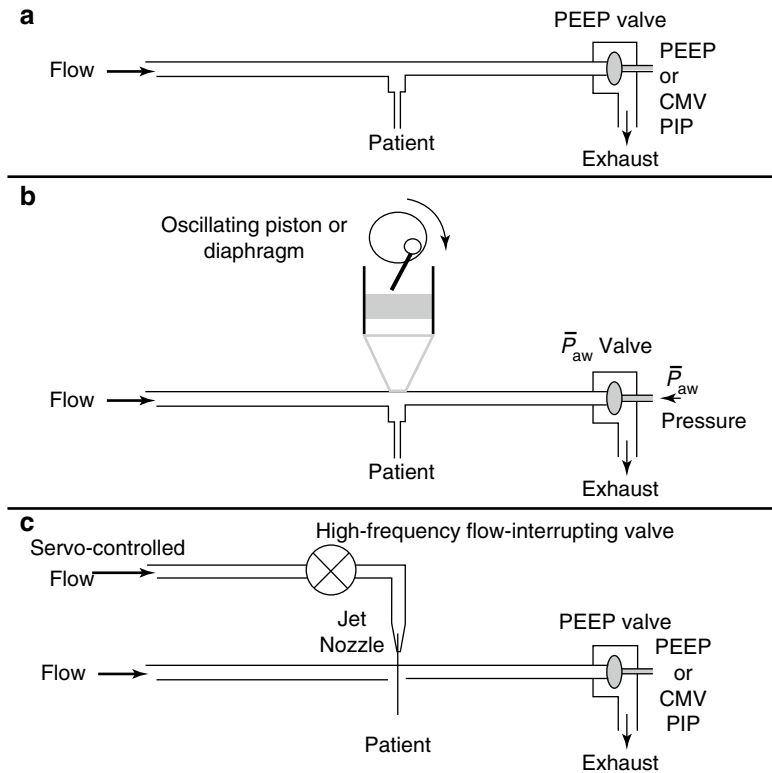


Fig. 8.47 Principles of gas delivery for different modes of ventilation: (a) During pressure-limited conventional ventilation, closure of the expiratory (*PEEP*) valve diverts the full bias flow to the patient circuit. Volume delivery to the patient is determined by the peak pressure that develops and the mechanical properties of the intubated respiratory system. During expiration, resistance through the expiratory (*PEEP*) valve determines the level of *PEEP* applied. Expiratory flow is determined by passive recoil of the chest and the resistance through the expiratory (*PEEP*) valve; (b) During high-frequency oscillatory ventilation, a constant bias flow is maintained across the circuit throughout inspiration and expiration. An oscillating piston or vibrating diaphragm diverts small parcels of this fresh bias flow to the patient circuit at high frequency. The oscillatory action of the piston/diaphragm results in active

inspiration and expiratory phases – such that expiration is independent of the chest recoil mechanics. Mean airway pressure is determined by the amount of resistance offered to egress of the bias flow through the mean airway pressure valve in the expiratory limb; (c) In high-frequency jet ventilation, the jet ventilator is coupled to a conventional ventilator. *PEEP* is determined by the resistance to flow through the *PEEP* valve generated by the conventional ventilator. Intermittent closure of the *PEEP* valve facilitates delivery of low rate conventional ventilator inflation as required for volume recruitment. A separate servo-controlled flow is interrupted at high frequency to send high-velocity small volume jets of fresh gas to the patient, accounting for more than 90 % of the fresh gas delivery, and is the principle determinant of the removal of carbon dioxide

pressure waveform can be generated by a piston moving back and forth, in continuity with the patient's airway, or by a variety of venturi and jet injector configurations. To be a true oscillator, the magnitude of the negative pressure wave deflection should be roughly equal to that of the positive pressure deflection when operating with equal inspiratory and expiratory cycle durations. Such matching of positive and negative pressure

deflections can be achieved by a linear motor piston pump, an electromagnetically driven vibrating diaphragm device or an expiratory venturi jet. Examples of contemporary piston HFO ventilators include the SM 3100A, SM 3100B, Humming V, the Flowline Dragonfly, the Heinen and Löwenstein Leoni plus, and the Stephan SHF 3000. The non-piston oscillators generally function much the same as piston oscillators; the

Table 8.16 Comparison of main features of CMV, HFOV, and HFJV

	CMV	HFOV	HFJV
Frequency (Hz)	0–2.5	3–15 ^a	4–11
$t_I : t_E$	3:1–1:300 ^a	1:2.5–1:1 ^a	1:12 to 1:3
t_I (s)	0.1–2 s ^a	0.02–0.17 ^a	0.02 (to 0.034)
Waveform	Variable	Square/sinusoidal/mixed	Peaked, complex
Exhalation	Passive	Active/venturi	Passive
CV needed	Yes	Not required	Yes
V_E and O_2 uncoupled	No	Yes	Partial
TT adapter	No	No	Yes

^aValues are given for the Babylog 8000+ (CMV) and the SM 3100A (HFOV) and may vary with different ventilators within a specific class of ventilation. t_I inspiratory time, t_E expiratory time, V_E ventilation, O_2 oxygenation, TT tracheal tube

variables that influence gas exchange, the mechanisms of gas exchange, as well as applicable ventilation strategies are very similar among these devices. Contemporary non-piston oscillators include the SLE5000, the Drager Babylog 8000+ (BL8000+), and the Babylog VN500.

For both piston and non-piston oscillators, each device has its own unique operating characteristics and limitations. It is therefore crucial that the clinician be familiar with the key features of each device. The differences between HFO ventilators and those that provide conventional pressure-limited ventilation or HFJV are shown in Fig. 8.47 and highlighted in Table 8.16. The important features of HFO ventilators include largely independent manipulation of oxygenation (via adjustments to mean airway pressure) and removal of carbon dioxide (via adjustments to oscillatory amplitude and frequency), and the active expiratory phase.

8.2.1.1.1.2 Ventilation

Ventilation at tidal volume (V_T) equal to or less than anatomical dead space can and does occur during HFOV, although in infants with more severe disease, the tidal volume is often slightly greater than dead space (Dimitriou et al. 1998). Whereas minute volume (respiratory rate $\times$ tidal volume) is the determinant of CO_2 removal when breathing at conventional breathing rates, the efficiency of gas mixing is greatly increased at breathing frequencies greater than 3 Hz, such that carbon dioxide elimination is more closely related to $f \cdot V_T^2$ (Slutsky et al. 1981; Slutsky 1984). The mechanisms responsible for this highly efficient ventilation during HFO were elegantly outlined

in the classic article by Chang (1984) and more recently by Slutsky and Drazen (2002) and are summarized in Fig. 8.48. Briefly, direct alveolar ventilation from bulk movement of gas occurs proximally. Turbulent flow also contributes to proximal gas transport. Asymmetric velocity profiles that occur due to the parabolic shape of gas moving back and forth in the airways enhance distal penetration of fresh oxygen-rich inspiratory gas and egress and radial mixing of CO_2 . Movement of gas between alveoli with differing time constants leads to out-of-phase mixing (pendelluft) in more distal units, further enhanced by collateral ventilation via pores of Kohn. Cardiogenic mixing may further enhance gas mixing, particularly in the left lingular and left lower lobe. Distally, where flow becomes more laminar, molecular diffusion occurs at the alveolar–capillary membrane (Khoo et al. 1984).

Tidal volume delivery can be influenced by both amplitude and frequency (decreasing as frequency increases) as well as by other circuit and mechanical properties of the intubated respiratory system, including the size of the ETT and airway resistance (Pillow et al. 2001). At high frequency, tidal volume is largely independent of compliance (except at very low compliance); however, tidal volume becomes increasingly dependent on lung compliance as frequency is decreased (Pillow et al. 2001).

Under normal conditions, HFO ventilation is characterized by marked damping of oscillatory pressure waveform by the relatively high impedance (resistance and inertance) associated with turbulent flow through the tracheal tube. The degree of that attenuation is principally

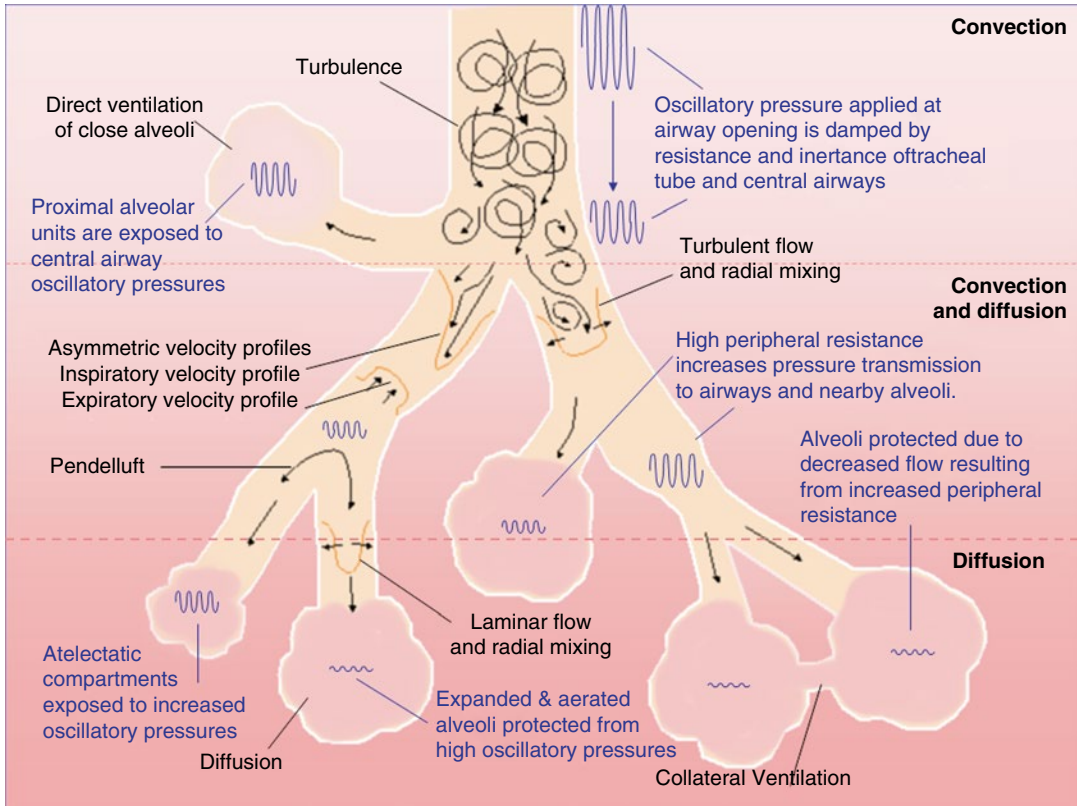


Fig. 8.48 Gas-transport mechanisms and pressure damping during high-frequency oscillatory (HFO) ventilation: The major gas-transport mechanisms operating during HFOV in convection, convection–diffusion, and diffusion zones include the following: turbulence, bulk convection (direct ventilation of close alveoli), asymmetric inspiratory and expiratory velocity profiles, pendelluft, cardiogenic mixing, laminar flow with Taylor dispersion, collateral ventilation between neighboring alveoli, and molecular

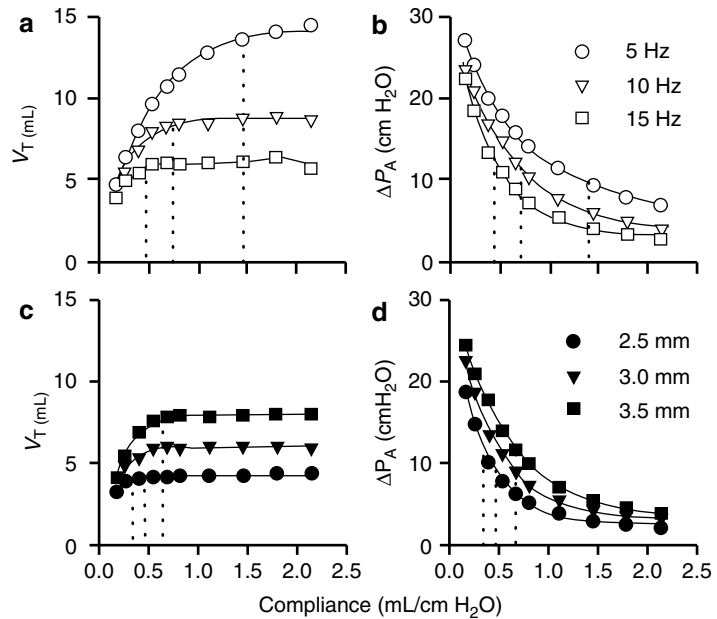
diffusion (see text for details). The extent to which the oscillatory pressure waveform is damped is influenced by the mechanical characteristics of the respiratory system. Atelectatic alveoli will experience higher oscillatory pressures than normally aerated alveoli, whereas increased peripheral resistance increases the oscillatory pressures transmitted to proximal airways and neighboring alveolar units (Adapted with permission from Slutsky and Drazen 2002)

determined by the internal diameter of the ETT and the frequency employed (Fig. 8.49). However, an often poorly appreciated fact is that the transmission of oscillatory pressure amplitudes to the lung can be markedly increased in the presence of abnormal lung mechanics. The main effects are summarized in Figs. 8.48 and 8.49.

The optimal frequency of ventilation will vary, therefore, according to the mechanical properties of the intubated respiratory system. Optimal frequency selection is best estimated by considering the oscillatory pressure cost of achieving flow (Venegas and Fredberg 1994): This falls rapidly with increasing frequency, reaching a minimum

at the resonance frequency of the lung. However, in overdamped lungs, minimal additional damping of the oscillatory pressure waveform is achieved above the corner frequency (f_c) of the lung: $f_c = 1/2\pi RC$ where R is the respiratory resistance and C is the lung compliance. Thus, there is benefit in increasing frequency up to, but not beyond, the corner frequency of the lung (Pillow 2005). Low-compliance lungs are optimally ventilated within a limited range of high frequencies, while lower frequencies are more appropriate in high-resistance systems, to avoid barotrauma to the proximal airways and neighboring alveoli while still achieving adequate volume delivery

Fig. 8.49 Effect of compliance on V_T and ΔP_A at different frequencies and ETT sizes: Graphs show tidal volume (V_T : **a**, **c**) and amplitude of the alveolar pressure waveform (ΔP_A : **b**, **d**) at different frequencies and tracheal tube sizes, using a mathematical model (Reproduced with permission from Pillow et al. 2002)



to effect adequate gas exchange. In contrast, a healthy lung will tolerate a wider frequency selection without significant injury.

8.2.1.1.1.3 Oxygenation and Optimal Lung Volume

Mean airway pressure is the primary determinant of oxygenation during HFO ventilation, and its appropriate selection to achieve optimal lung distension (avoiding atelectasis and overdistension) is a critical consideration in minimizing the pressure and flow cost of ventilation during HFO ventilation (Venegas and Fredberg 1994). Mean pressure measured at the airway opening (patient connector – P_{ao}) is used as an approximation of mean airway pressure; however, this may overestimate mean airway pressure when $t_I:t_E$ ratios less than 1:1 are used (Pillow et al. 1999; Gerstmann et al. 1990; Thome and Pohlandt 1998), and the magnitude of this pressure drop will increase with decreasing ETT size and increasing frequency (Pillow et al. 1999) (Fig. 8.50).

Optimal P_{ao} is attained when fractional inspired oxygen (FiO_2) is at a minimum, and the chest radiograph shows maximal resolution of atelectasis without evidence of hyperinflation. Clinically, this point is best obtained at initiation of HFOV in an atelectatic lung by focused

volume recruitment maneuvers. The most common approach is to increase the P_{ao} and to wean the FiO_2 according to peripheral oxyhemoglobin saturations (SpO_2) until the FiO_2 reaches a minimum value then starts to increase. P_{ao} is then decreased until FiO_2 is again at minimum. At this point the lung is being ventilated at the point of maximum curvature on the descending limb of the pressure–volume curve, often referred to as “optimal lung volume” (see Fig. 8.51). An alternative approach is to use “sigh” recruitment maneuvers to raise the resting volume of the lung up to optimal lung volume. Videomicroscopy illustrates clearly how the use of a constant distending pressure sufficient to keep the airways and alveoli open throughout the respiratory cycle potentially avoids atelectotrauma that may occur more easily when using conventional ventilator modes (see Fig. 8.52).

An accurate and easy-to-use bedside measure of distending lung volume during HFOV is desperately needed. Current methods used in research and clinically in selective units include electrical impedance tomography and respiratory inductance plethysmography (Wolf and Arnold 2005). Indirect measures including nonlinear lung mechanics (Habib et al. 2002), intermittent oscillatory mechanics (Pillow et al. 2004),

Fig. 8.50 Effect of ventilator settings and respiratory mechanics on mean pressure drop: Graphs illustrate the magnitude of the difference in mean pressure between the airway opening and the lung (P_{diff}) attributable to change in ventilation frequency (a), % inspiratory time (b), endotracheal tube internal diameter (c), or lung compliance (d) in an in vitro model lung (Reproduced with permission from Pillow et al. 1999)

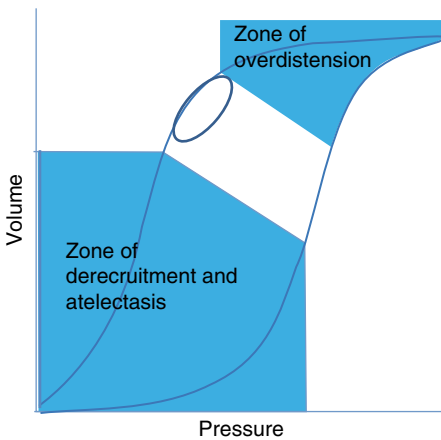
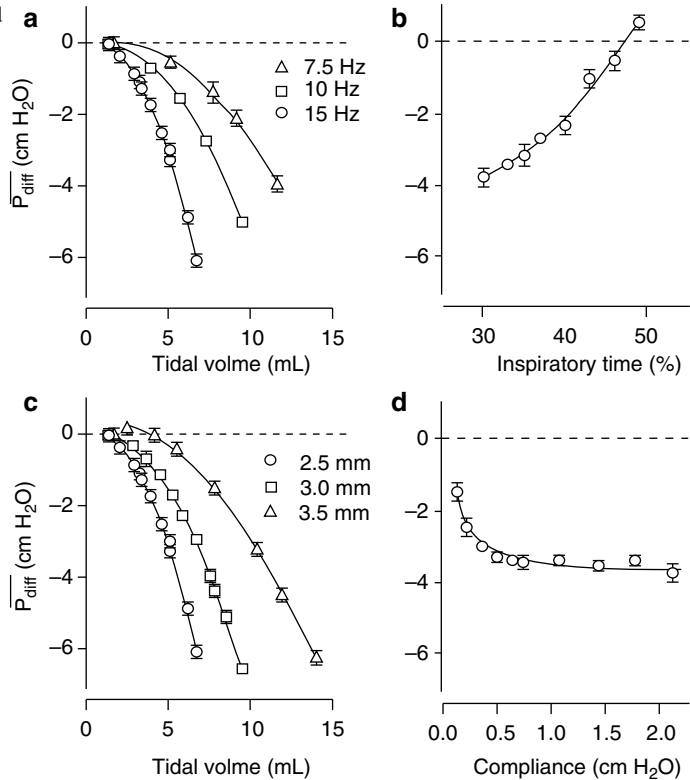


Fig. 8.51 Zone of ventilator-induced lung injury (VILI) relative to distending lung volume: Small cyclic volume changes at the point of maximal curvature on the deflation limb of the volume–pressure relationship may protect the lung from injury arising from overdistension (volutrauma) or atelectasis (atelectotrauma) (Reproduced with permission from Froese 1997)

and measurement of the oscillatory pressure ratio (OPR) can also identify the optimal lung volume

(van Genderingen et al. 2002) (see Fig. 8.53). Of each of these methods, the oscillatory pressure ratio (ratio of tracheal pressure amplitude to airway opening pressure amplitude: $\Delta P_{\text{tr}} / \Delta P_{\text{ao}}$) is likely to be the most easily achieved at the bedside in a wide range of clinical units – but requires the measurement of ΔP_{tr} , which is not yet a routine measurement in the NICU.

8.2.1.1.2 Contemporary HFO Ventilators

8.2.1.1.2.1 Piston HFO Ventilators

A range of contemporary piston HFO ventilators are available for clinical and research use. They differ with respect to generation of oscillatory flow, frequency, amplitude, mean airway pressure, inspiratory to expiratory ratio, monitoring options, and integration with a conventional ventilator.

Sensor Medics

The SensorMedics 3100A (SensorMedics, CareFusion, San Diego, CA) is indicated for use in neonates and children less than 35 kg.

Fig. 8.52 Videomicroscopy of alveolar morphology during conventional ventilation and HFO ventilation: Figure shows subpleural alveoli in the rat after lung injury by saline lavage ventilated with either conventional mechanical ventilation (CMV) or high-frequency oscillatory (HFO) ventilation. With CMV, alveoli inflated during inspiration (dots, panel a) collapse with expiration (arrows, panel b). In contrast, alveoli remain open and stable with HFO ventilation throughout inflation (panel c) and exhalation (dashes, panel d) (Reproduced with permission from Carney et al. 2005)

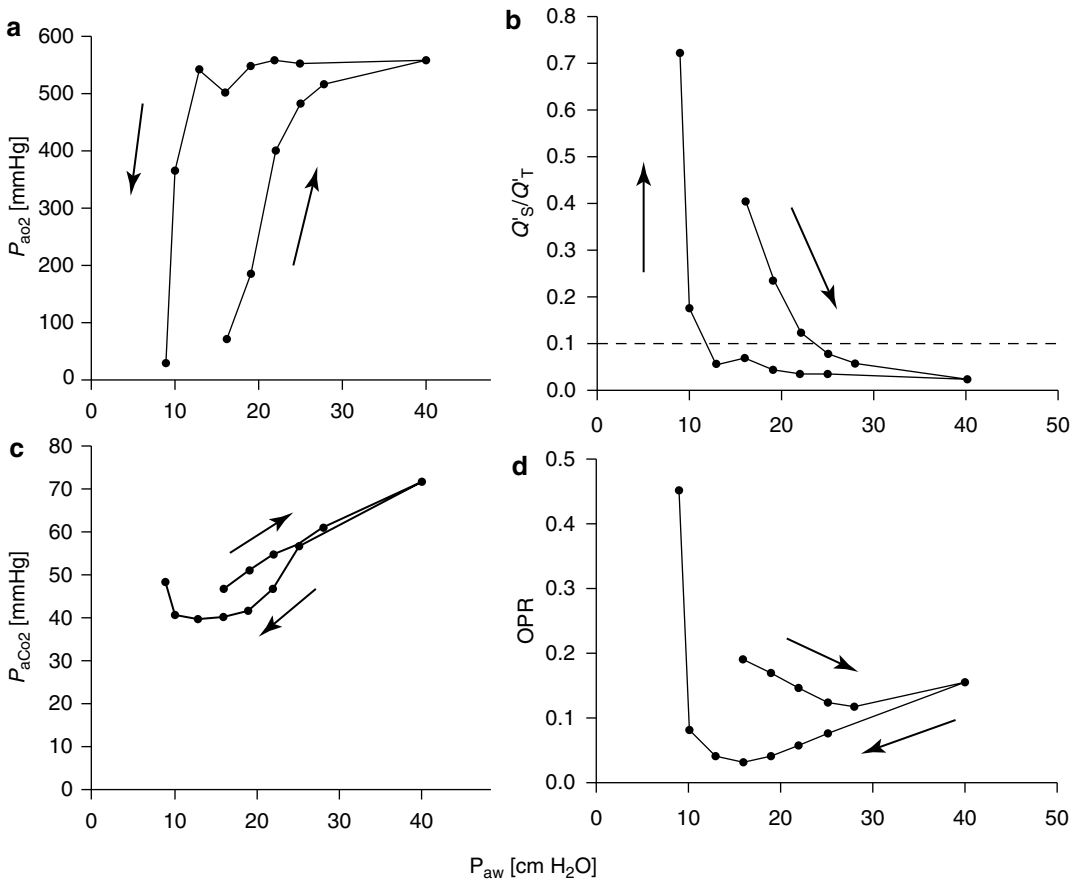
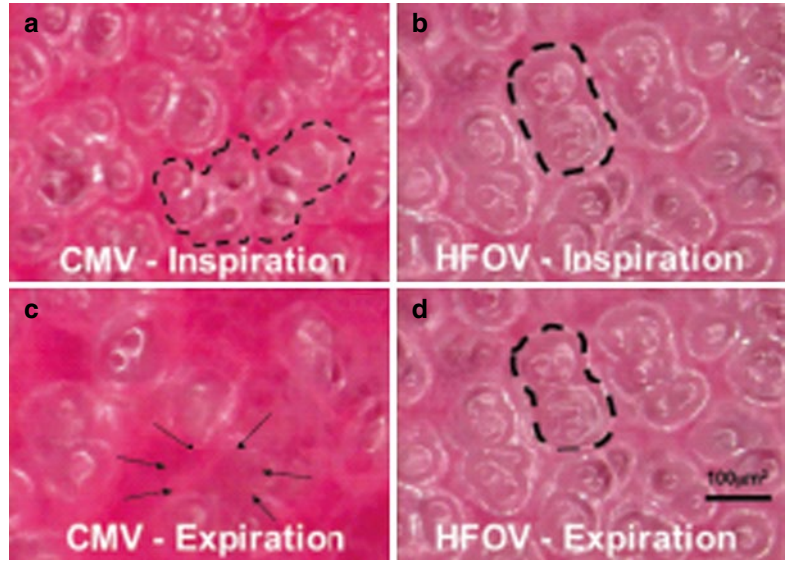


Fig. 8.53 Relationship between P_{aw} and (a) P_{aO_2} , (b) physiological shunt fraction, (c) P_{aCO_2} , and (d) oscillatory pressure ratio: The arrows indicate the order in which values change in response to increments and subsequent decrease in P_{aw} . The minimum oscillatory pressure ratio

(OPR: $\Delta P_{tr}/\Delta P_{aw}$ where ΔP_{tr} is tracheal pressure amplitude and ΔP_{aw} is airway pressure amplitude measured at airway opening) coincides with optimum P_{aCO_2} , P_{aO_2} , and minimum physiological shunt fraction (Q'_s/Q'_T) (Adapted from van Gendingen et al. 2002)

An electromagnetic piston diaphragm is oscillated back and forth, very similar to a permanent magnet loudspeaker. It produces a complex square pressure waveform with multiple frequency harmonics. The ventilator is the most powerful stand-alone neonatal oscillator and cannot be used as a conventional ventilator. Capabilities include a frequency range of 3–15 Hz, proximal amplitudes of 10–110 cm H₂O, and mean airway pressures of 3–45 cm H₂O using bias flow of 3–40 L/min. Mean airway pressure is achieved by a continuous bias flow of gas past the resistance (inflation) of the balloon on the mean airway pressure-control valve. Inspiratory time is set as percent of the duty cycle; it can be varied from 30 % to a maximum of 50 %; however, the manufacturer recommends using 33 % as few data are available on the safety of using 50 % with this device. There is no facility for a sigh maneuver; hence, volume recruitment with the SM 3100A requires adjustments to the mean airway pressure. The current commercially available ventilator does not provide demand flow, which can interfere with spontaneous breathing efforts. Tidal volume is not monitored. Operative noise levels are relatively high compared to most other HFOV ventilators.

The SensorMedics 3100B is indicated for use in children and adults greater than 35 kg, though it can also be used in neonates and small children. It functions similarly to the 3100A, though it is much more powerful. Bias flow capability of up to 60 L/min allows provision of P_{aw} of 5–55 cm H₂O and amplitudes of >90 cm H₂O in adult patients. Frequency range is 3–15 Hz and inspiratory time can range from 30 to 50 % of the duty cycle. Tidal volume is not monitored.

Metran Ventilators

The Hummingbird oscillators are the most well-known oscillators produced by Metran (Saitama, Japan). They are piston oscillators (linear motor generators) with inspiration and expiration each accounting for 50 % of the duty cycle. The Humming V (current model) can function as both a conventional ventilator (SIMV) and an oscillator. The HFO pressure waveform is sinusoidal. During HFOV, frequency range in the Humming V is

limited to 13–17 Hz which limits its application in situations of high resistance (e.g., meconium aspiration). Inspiratory to expiratory time ratio is limited to 1:1 (although can be changed to 1:3 by altering dip switch settings). The Humming V has an output equal to that produced by the SM 3100A (Pillow et al. 2001; Hatcher et al. 1998). Sighs can be delivered manually or programmed to be delivered as infrequently as once every 5 min. Synchronized breathing is easier on the Humming V than with the SM 3100A. Tidal volume is not monitored.

More recently, Metran has produced two other HFO ventilators including the Calliope α and the R100 (or Vision α in Europe by Novalung GmbH, Talberg, Germany). The Calliope α provides enhanced mean airway pressure capabilities (up to 40 cm H₂O), smaller adjustments of stroke volume, a wider frequency range (5–17 Hz), and quieter operation and includes PSV as a conventional ventilation mode. The R100 (Vision α) offers both CMV and HFOV. The new rotary valve associated with the R100 (or Vision α) produces square wave oscillations sufficiently powerful to be used not only in small children (≥ 5 kg) but also in adults. Capabilities include a frequency range of 5–15 Hz, oscillatory stroke volumes (that are to be set by the operator instead of a pressure amplitude) that range from 2 to 350 mL (and vary with the oscillatory frequency), and mean airway pressures of 5–60 cm H₂O. Operative noise levels are very low compared to the SensorMedics 3100 A and B.

Stephan

Stephan-GmbH (Gackenbach, Germany) offers two neonatal ventilators capable of HFO, those being the Stephanie and the Sophie ventilators. Both are combined conventional/HFO ventilators and have the same HFO performance. Adjustable settings include waveform (Stephanie, square or sinusoidal; Sophie, square only), frequency (5–15 Hz), inspiratory to expiratory time ratio (Stephanie 1:1, 2:3, 1:2; Sophie from 1:1 to 1:2), and mean airway pressure (maximum P_{aw} 30 cm H₂O). Stroke volume is somewhat more limited (max stroke volume of 20 mL) than the abovementioned HFO ventilators, limiting their HFO use to infants up to 10 kg. Combined HFO and conventional ventilation is possible. Tidal volume is monitored.

Heinen + Löwenstein

Heinen + Löwenstein (Bad-Ems, Germany) offers the Leoni plus which is a neonatal ventilator capable of HFO and CMV. The integrated HFO module works according to the diaphragm principle (double membrane). The waveform is sinusoidal. Adjustable settings include frequency (5–20 Hz), inspiratory to expiratory time ratio (1:1, 2:3, 1:2, 1:3), and mean airway pressure (maximum P_{aw} 40 cm H₂O). Stroke volume is somewhat more limited than the abovementioned HFO ventilators, limiting its HFO use to infants up to 10 kg. Combined HFO and conventional ventilation is possible with oscillation provided during the inspiratory and expiratory cycle. Tidal volume is monitored. The requirement for a pressure supply of 2.0–6.5 BAR (29–63 PSI), low gas-flow requirements of 7 L/min to support the mean airway pressure, and an inbuilt battery (30 min backup in the HFO mode, 1-h backup in the CMV mode) allow for short intrahospital transfer (e.g., NICU to operating theater).

Acutronic

Acutronic Medical Systems (Hirzel, Switzerland) offers the Fabian HFO which provides HFOV in addition to CMV for neonates and children up to 30 kg. The integrated HFO module works according to the diaphragm principle (large single membrane). The waveform is sinusoidal. Adjustable settings include frequency (5–20 Hz), inspiratory to expiratory time ratio (1:1, 1:2, 1:3), mean airway pressure (maximum P_{aw} 40 cm H₂O), and amplitude settings from 5 to 80 cm H₂O. During HFOV, a volume guarantee mode can be chosen in the tidal volume range of 1–30 mL (suitable for patients up to 10 kg). Combined HFO and conventional ventilation is possible with oscillation provided during the inspiratory and expiratory cycle. Tidal volume is monitored. The requirement for relatively low pressure supply (< 2.0 BAR/< 29 PSI), a low base flow of only 2–10 L/min, an inbuilt battery (1-h backup in the HFO mode, 4-h backup in the CMV mode), and a relative low unit weight (only 18 kg) allows for intrahospital (e.g., NICU to operating theater) and short interhospital (e.g., ambulance and air ambulance) transfers.

Flowline

The Dragonfly (Shreeyash Electro Medical, India) represents the start of a new generation of HFO ventilators. Offering servo-controlled bias flow, mean airway pressure, and piston positioning, it is a more user-friendly option for the clinician due to reduced need for manual adjustment and correction of ventilator settings, which otherwise may change in response to alterations to any one of these factors. It offers a frequency range of 5–18 Hz and inspiratory to expiratory time ratios of 1:2 and 1:1. Bias flow is adjustable from 4 to 60 L/min and mean airway pressure is servo controlled up to 40 cm H₂O. It is a moderately powerful ventilator with a maximum piston volume of up to 500 mL. Tidal volume is monitored. The requirement for low pressure supply (only 1.5 PSI) and an inbuilt battery (2-h backup) facilitates the use of the ventilator for intrahospital transfers (e.g., NICU to operating theater).

8.2.1.1.2.2 Non-piston HFO Ventilators

Babylog 8000+

The BL8000+ (Draeger, Lubeck, Germany) is a device capable of producing both conventional and high-frequency oscillatory ventilation alone or in combination. During HFOV, mean airway pressure and the positive pressure deflection of the oscillatory waveform are generated by continuous flow of gas from a bank of precision solenoid valves. The inspiratory flow is automatically adjusted based on choice of mean airway pressure (maximum of 25 cm H₂O) and frequency (5–20 Hz). Superimposed on this is an intermittent negative pressure generated by a venturi effect of the high-flow jet injector at the expiratory valve causing active exhalation. Thus, circuit pressure fluctuates from positive to negative based on the activation of the expiratory valve venturi. The inspiratory flow is not interrupted during the expiratory phase; it is overcome by the negative pressure of the active expiratory flow. Therefore, the BL8000+ is clearly NOT a flow interrupter, although it has commonly been described as such. The $t_I:t_E$ ratio is not directly set, but is a function of the set frequency, varying from 1:1 at 15 Hz to as much as 1:5 at the lowest

frequencies. At the typical frequency of 8–10 Hz, the ratio is close to 1:2. The amplitude is set as a percentage of peak output, which is calculated as a percentage of the difference between mean airway pressure and 60 cm H₂O. For example, if the mean airway pressure is 15 cm H₂O, then 100 % amplitude would be 45 cm H₂O with a pressure range from –7.5 to 37.5 cm H₂O. However, the actual amplitude is limited at low mean airway pressure by a safety limit valve that does not permit the negative pressure to drop below –4 cm H₂O. The practical consequence of this is that once the trough pressure reaches –4 cm H₂O, further increases in % amplitude do not increase delivered tidal volume, unless the mean airway pressure is also increased. The effective amplitude is very frequency dependent. Limited tidal volume is produced at frequencies above 10 Hz; therefore, in larger infants, frequencies below 8 Hz may be needed to achieve adequate tidal volume. The waveform is a true sinusoidal waveform with equal positive and negative deflection at 1:1 ratio and quasi-sinusoidal at the shorter inspiratory ratios. The device monitors tidal volume (V_T) during HFOV using a hot wire anemometer at the airway opening; this is a distinct advantage over some commonly available HFV devices. A calculated value of DCO₂ (rate of CO₂ removal) is displayed, allowing the clinician to easily recognize changes in minute ventilation.

VN500

Virtually all the limitations of the BL8000+ were effectively addressed in the recently released (late 2009) Draeger VN500. The new device is much more powerful, reaching 80 % of the output of the SensorMedics 3100A in bench tests at 5 Hz using optimal circuit configurations (J Pillow, unpublished data, 2012). In the VN500, the circuit inflow is actively modulated during the expiratory phase, and the larger, reconfigured expiratory valve is capable of generating much stronger active exhalation. The $t_I:t_E$ ratio is now user controlled in the range of 1:1 to 1:3. The pressure amplitude is set directly by the user and is no longer a percentage of an abstract maximum value. The –4 cm H₂O safety valve is neutralized during HFOV, allowing the device to generate large

amplitudes even at low mean airway pressure. However, mean airway pressure should not be too low or atelectasis will develop as with any form of ventilation. Additionally, as in all devices, airway collapse can potentially result from active exhalation at low mean airway pressure and this could lead to air trapping. Inappropriately low mean airway pressure should therefore be avoided. Conventional sigh inflation can be combined with HFOV to aid in lung volume recruitment.

An important new development is the ability to servo control the delivered V_T (measured as exhaled tidal volume at the airway opening) by means of HFOV + Volume Guarantee (VG) option. This allows the user to preset a V_T during HFOV, much like with conventional volume guarantee. It should be noted that activating VG eliminates the effect of changes in frequency on delivered VT seen in other HFOV devices. The calculated value of DCO₂ (rate of CO₂ removal) is displayed as in the 8000+. As with other HFOV devices intrahospital transport is possible. Due to its very recent release, there are no clinical studies at this time to support the clinical benefits of the new Draeger VN500 high-frequency oscillator.

SLE 5000

The SLE 5000 (SLE corporation, South Croydon, UK) is also a combination conventional and high-frequency ventilator. Continuous flow of heated, humidified gas at 8 L/min in the ventilator circuit is opposed by a reverse jet of gas in the expiratory block, resulting in positive end-expiratory pressure. Adjustment of the gas flow controls the mean airway pressure. Oscillations are produced at the expiratory block by a rotating ball valve that directs a second jet alternately against the continuous gas flow or with it, resulting in positive and negative pressure deflections, in essence acting as a pneumatic piston. This design results in a fixed 1:1 inspiratory to expiratory ratio and results in a true sinusoidal waveform with active exhalation. The device is sometimes referred to as a “valveless jet ventilator,” but that is a misleading term, because the jet does not reach the patient and does not directly participate in gas exchange. Frequency is adjustable from 3 to 20 Hz. Airway opening pressure amplitude (ΔP_{ao}) range is

4–180 cm H₂O and mean airway pressure range is 4–35 cm H₂O. Oscillations can be delivered in isolation or superimposed on conventional inflation which may be patient triggered. The manufacturer claims the ability to support infants from 300g to 20 kg, depending on lung mechanics. Tidal volume is monitored. The inbuilt battery (1-h backup) allows the use of the ventilator for intrahospital transfers.

8.2.1.1.3 Performance Characteristics of HFO Ventilators

Several *in vivo* and *in vitro* studies have highlighted important differences in performance characteristics between different HFO ventilators (Pillow et al. 2001; Hatcher et al. 1998; Fredberg et al. 1987; Jouvet et al. 1997). An understanding of these differences is essential for clinicians treating patients with HFO. In particular, it is important for practitioners to know the specific characteristics and capabilities of (and differences between) the machine(s) used in their unit. For example, the Humming V has a limited frequency range, and thus, volume output is limited, which in turn limits the size of the patient for whom this machine can be used. It also limits the applicable clinical situations given that lower frequencies may be needed when airway resistance is high (Pillow 2005; Hatcher et al. 1998).

Utilization of an inspiratory to expiratory time ratio less than 1:1 (e.g., 1:2) (SM 3100, Stephanie, Sophie, Leoni Plus, BL8000+ and VN500, Dragonfly) may produce mean intrapulmonary pressures that are lower than those at the airway opening (Pillow et al. 1999; Gerstmann et al. 1990; Thome and Pohlandt 1998; Hatcher et al. 1998). This arises due to flow dependence of resistance through the tracheal tube and the increased inspiratory resistance relative to expiratory resistance seen assuming airways are stented open by use of sufficient mean airway pressure (removing the normal increased resistance associated with partially collapsed airways at low PEEP in conventional ventilation). Contrary to widely held beliefs, with an inspiratory to expiratory time ratio of 1:1, mean intrapulmonary pressure is very similar to that displayed at the airway opening during HFOV provided that sufficiently

high mean airway pressures are employed to avoid choke point formation (Pillow et al. 1999; Hatcher et al. 1998). Differences in algorithms used for tidal volume calculation may also result in overestimation (SLE 5000) or underestimation (Stephanie) of the delivered volume by between 5 and 20 %, and the inaccuracy of this display may also increase as frequency is increased (Leipala et al. 2004).

A further important consideration is the nature of the ventilator circuit. Unlike the SM 3100 and the Dragonfly, the Stephan and Metran piston oscillators and the non-piston oscillators use a conventional ventilator circuit. This means that ventilator circuits and humidifiers need to have minimal compliance and compressible volume; nonstandard circuits and humidifiers could adversely affect performance. A potential advantage of ventilators capable of both conventional and HFOV is the option of combining low rate of conventional sighs with HFOV, which may be useful in maintaining an open lung strategy without excessive mean airway pressure. However, the benefits of this strategy have not been systematically evaluated.

8.2.1.1.4 HFO Ventilator Developments and Future Directions

Many sick newborns require transport to other institutions for surgery, extracorporeal membrane oxygenation (ECMO), or other special care. If these infants have already been started on HFO, transporting them on conventional ventilation may not be tolerated. Current oscillators are not configured for use in transport, requiring a change to a jet ventilator (Bunnell Life Pulse) or flow interrupter (Bronchotron), both discussed later in this chapter. An oscillator that could be used for transport would be an important future development. While intrahospital (e.g., ICU to theater) transport is now possible (Dragonfly, VN500, Leoni plus, Fabian HFO), further research and development is required to provide a reliable ventilator for long-distance interhospital transfers. Incorporation of low gas pressures and flows into such a ventilator would be an important consideration.

Although HFOV has been in clinical use for 25 years, many issues relating to optimum clinical application still remain to be resolved. Focus

on inspiratory to expiratory ratio has largely related to gas trapping and intrapulmonary pressures, but this aspect may also have implications for gas-transport efficiency and shear stress, due to differences in inspiratory and expiratory flow profiles. It is also unclear whether the complex frequency content of a square pressure waveform offers specific advantage/disadvantage over a sinusoidal waveform. The optimal method of volume recruitment (sigh versus increased mean airway pressure) is also unclear. Finally, increased awareness of the lack of patient-initiated breathing and stretch on diaphragm dysfunction have highlighted the desirability of allowing superimposition of HFO on gentle spontaneous breathing movements without additional sedation. Therefore, enhanced patient–ventilator interactions need to be a focus of future HFO ventilator development.

New ventilators are constantly being developed, and by the time this book is in press, almost certainly new machines capable of providing HFO will be available. As these new ventilators emerge, it is important that their performance characteristics are fully evaluated and that the practitioner understands the machine being used and how it may differ from other HFO ventilators, in order to optimize patient care.

8.2.1.2 High-Frequency Jet Ventilators

High-frequency jet ventilation is a distinct form of high-frequency ventilation that has been widely used in newborn infants for more than 25 years. It shares the basic principles of gas exchange with other HFV devices but differs in some important ways, which will be discussed in detail below. The “Sanders bronchoscope jet” was the first practical device that used the basic principle of jet ventilation and thus is the true forerunner of modern jet ventilators. This simple device was based on an observation that when oxygen was delivered via the side arm of a bronchoscope in short bursts rather than continuously, the CO₂ accumulation that previously limited bronchoscopy to only a few minutes was markedly reduced (Sanders 1967). True HFJV was first applied in adults in the mid-1970s using an electronically controlled solenoid valve jet ventilator (IDC

VS-600, Instrument Development Corporation, Pittsburgh, Pennsylvania) (Klain and Smith 1977). Subsequently, this device and two prototype jet ventilators based on fluidic technology were used in newborn infants in the early 1980s (Pokora et al. 1983). The initial application was in severely ill infants who were failing conventional ventilation and typically suffered from severe air leak complications (Spitzer et al. 1989). The emphasis was on reducing airway pressure, something for which HFJV is uniquely suited because of the very short inspiratory time and relatively long expiratory time. As treatment expanded to less severely affected infants and different disease processes, new strategies evolved that were more appropriate for these pathophysiologies (Keszler and Durand 2001). This section will focus on the Bunnell Life Pulse ventilator, because it is the only jet ventilator that is widely used and approved by regulatory agencies and for the treatment of newborns and young infants. The device is currently almost exclusively used in North America, although small numbers of these ventilators are in use in Europe and Australia.

8.2.1.2.1 HFJV: Principles of Functioning and Gas Exchange

HFJV shares the basic principles of gas exchange with other HFV devices, specifically the use of rapid respiratory rate and very small tidal volume. Mean airway pressure is the key determinant of oxygenation and CO₂ elimination is proportional to $f \cdot V_T^2$. However, the different mechanisms by which these devices generate high-frequency pulses or oscillations lead to some important differences in their function.

Unique to HFJV is the concept of spike formation. Henderson first described this phenomenon nearly 100 years ago (Henderson et al. 1915). He demonstrated that a high-velocity impulse of gas penetrates through the dead-space gas resident in the upper airway, rather than pushing it ahead, as occurs with gas flow at low velocities. Spike formation enhances bulk flow of gas in the upper airway by largely bypassing anatomical dead space and provides more efficient gas mixing in the more distal lung. Enhanced

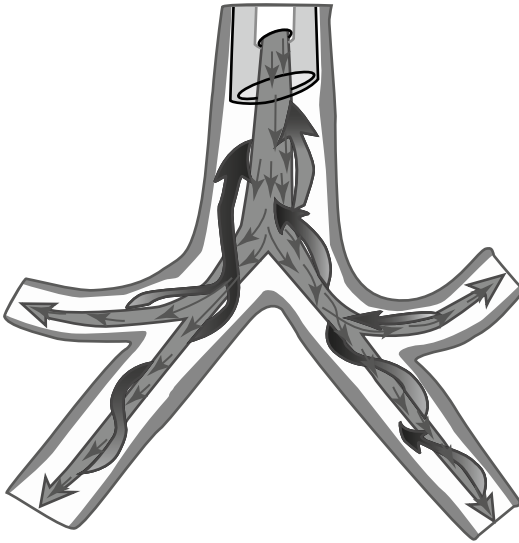


Fig. 8.54 Schematic of gas transport during HFJV. The diagram illustrates the principles of gas transport through the major airways during HFJV with a central high-velocity inspiratory jet stream, and the spiraling of expiratory gases in the reverse direction around this central inspiratory gas stream. The unique “spike” of gas penetrates the dead space of the upper airway, rather than pushing dead space ahead of it, as occurs with conventional ventilation at lower frequencies

molecular diffusion probably plays an important role in the gas exchange occurring in the distal airways and alveoli. Mathematical models predict and empirical observations support the concept that exhalation to a significant degree is concurrent with inspiration; high-velocity gases stream down the center of the larger airways with outward coaxial rotational flow occurring simultaneously (see Fig. 8.54). Bidirectional flow is likely the mechanism responsible for the ability of the jet ventilator to prevent aspiration, enhance clearance of meconium from the upper airways, and achieve effective alveolar ventilation even in the face of large airway disruption, as well as its ability to allow for faster resolution of pulmonary interstitial emphysema (Keszler et al. 1991). The position and curvature of the endotracheal tube appears to be important in the efficiency of spike formation and gas mixing. Other factors that reduce the effectiveness of spike formation and impair ventilation include the presence of thick secretions and debris in the airways.

The jet ventilator has a set inspiratory time (t_i), unlike HFOV where the inspiratory time is a fixed percentage of the respiratory cycle. Therefore, as the Life Pulse rate is adjusted, the only thing that changes is exhalation time. The frequency dependence of pressure amplitude and tidal volume seen with oscillatory-type devices is less problematic with HFJV, except at very low compliance (Pillow J., personal communication, 2010). The exhalation is passive; therefore, the optimal operating frequency of the jet ventilator is lower than that for HFOV and, as with other ventilators, needs to be lowered further in patients with prolonged time constants.

It is important to recognize that because of the extremely short inspiratory to expiratory time ratio ($t_i:t_E$), mean airway pressure ($\bar{P}_{aw}$) with the Life Pulse ventilator is primarily determined by the positive end-expiratory pressure (PEEP). Therefore, at equivalent peak inflation pressure (PIP), the PEEP must be substantially higher to maintain the same $\bar{P}_{aw}$ as on conventional ventilation and to prevent atelectasis in patients with atelectasis-prone lung disease. Failure to recognize this fact is the reason why HFJV acquired an unjustified reputation for being poor at achieving good oxygenation. While $\bar{P}_{aw}$ is predominantly determined by PEEP, it also receives a contribution from the HFJV peak insufflation pressure: Thus, $\bar{P}_{aw}$ and therefore oxygenation is not independent of ventilation. A reduction in HFJV ΔP_{aw} may need to be achieved by decreasing the HFJV peak insufflation pressure in parallel with an increase in positive end-expiratory pressure, if simultaneous weaning of $\bar{P}_{aw}$ is not desired.

The ability to combine conventional sigh or background inflations with HFJV is a potential advantage of the technique over some HFOV ventilators. Sighs are useful in initial lung volume recruitment and perhaps in maintenance of optimal lung inflation with slightly lower $\bar{P}_{aw}$. Once good lung volume has been achieved, the rate should be reduced to no more than 2 sighs/min or the sighs may be discontinued altogether. Background IMV at a higher rate is used by some clinicians to compensate for low mean airway pressure, but that is clearly a more injurious way of ventilation and therefore this practice should be discouraged.

8.2.1.2.2 Contemporary HFJ Ventilators

The Bunnell Life Pulse is the most widely used infant HFJV device. There are also several niche devices used infrequently in pediatric patients (Paravent, Chirajet, Monsoon).

8.2.1.2.2.1 Bunnell Life Pulse

The Bunnell Life Pulse HFJV (Bunnell Inc. Salt Lake City, UT) delivers short pulses of heated and humidified gas at high velocity to the upper airway through a narrow injector lumen in the LifePort adapter. This is a special 15-mm endotracheal tube adapter that contains a proximal jet injector port and a distal pressure monitoring port, eliminating the previous need for reintubation with a triple lumen endotracheal tube (Figs. 8.55 and 8.56). The clinician sets the same variables on the front panel of the Bunnell Life Pulse HFJV as he or she is accustomed to setting on conventional ventilators, namely, peak insufflation pressure (PIP, range 8–50 cm H₂O), respiratory rate or frequency (range 240–660 cycles/min or 4–11 Hz), and jet valve “on time,” which is comparable to inspiratory time (range 0.020–0.034 s). The Life Pulse $t_I:t_E$ varies from 1:3.5 at 660 cycles/min to 1:12 at 240 cycles/min (Harris and Bunnell 1993).

When introduced in the mid-1980s, the Life Pulse was the first microprocessor-controlled infant ventilator. Servo control of PIP is accomplished by the ventilator’s microprocessor, which compares the PIP level set by the operator with the actual PIP measured continuously in the distal airway and the driving or “servo” pressure behind the inspiratory pulses is raised or lowered in proportion to the difference between the set and actual PIP. These moment-to-moment adjustments in servo pressure are accomplished by an array of precision solenoid valves supplying the pressure chamber that supplies gas to the jet circuit.

Actual delivery of the jet pulses is by way of an electromagnetically controlled pinch valve in the “patient box” controlled by the same microprocessor. Moving the pinch valve and pressure transducer into the patient box placed close to the patient was an important advance, resulting in much less dampening of the jet pulse and more accurate pressure monitoring. More efficient jet



Fig. 8.55 Bunnell Life Pulse HFJ ventilator

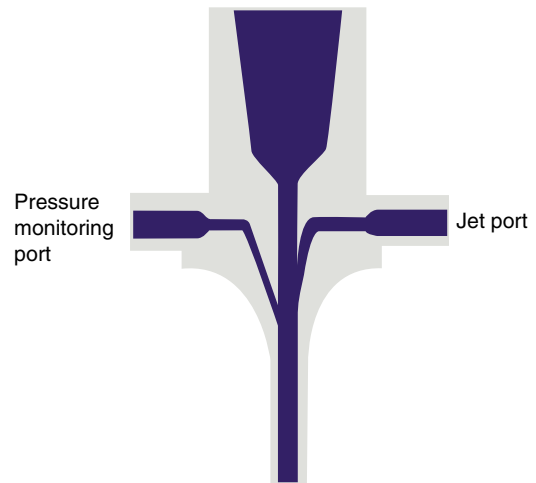


Fig. 8.56 LifePort adapter. The schematic shows the narrow injector port used to inject high-velocity small volume gas jets into the patient airway. The adapter includes a pressure monitoring port

pulse delivery allows the ventilator to operate efficiently at much higher frequencies and smaller tidal volume than the early prototype jet ventilators. The humidification system for the ventilator is also feedback controlled for maintaining appropriate temperature, humidity, and water level. The temperature of the humidification cartridge and circuit can be adjusted independently to prevent excessive condensation. The disposable humidifier cartridge and circuit are designed to withstand

the relatively high servo pressure and have a very small compressible volume. Prior to the introduction of this efficient heating and humidification system, inadequate humidification of inspired gas with prototype HFV devices resulted in a series of reports of necrotizing tracheobronchitis that led to a temporary dampening of enthusiasm for HFJV (Ophoven et al. 1984).

A conventional ventilator is used in tandem with the Life Pulse and serves as a source of bias gas flow for entrainment and to generate positive end-expiratory pressure (PEEP). When desired, it also provides intermittent sighs in the form of background intermittent mandatory ventilation (IMV) inflations, typically at a rate of two to ten inflations per minute. The amplitude of the HFJV pulses is determined by the difference between the jet peak insufflation pressure and the conventional ventilator PEEP. The FiO_2 of the two ventilators is adjusted separately but should be maintained at the same value. The actual PIP, $\bar{P}_{\text{aw}}$, ΔP_{aw} , and servo pressure are displayed in the monitoring window on the face of the ventilator. Alarms are automatically set 15 % above and below current levels for PIP, $\bar{P}_{\text{aw}}$, and servo pressure once the values stabilize and the ventilator reaches the “Ready” state. Subsequently, the alarm limits can be adjusted manually.

8.2.1.2.2.2 Paravent PAT Ventilator

The Paravent PAT ventilator (Elmed, Prelouc, Czech Republic) has been in limited use in Europe for some time (Zahorec et al. 2009). It is a pneumatically controlled high-frequency jet ventilator with a distally located jet nozzle and a constant frequency of 120 inflation/min. This device is primarily used for short-term procedures, such as laryngeal surgery, bronchoalveolar lavage, and endobronchial procedures in adults and children. The gas is delivered through the multinozzle jet injector that is available in different sizes and has three inspiratory jets with different degrees of pressure reduction. Insufflation pressure, ratio of inspiratory to expiratory time ($t_i:t_E$: 1:2, 1:1, and 2:1), and ventilating pressure limit are set. Airway pressure is monitored through a catheter connected to the jet injector. There is no heating or, humidification of inspired gas.

8.2.1.2.2.3 Chirajet Ventilator

The Chirajet (Chirana, Stará Turá, Slovakia) has been used primarily for laboratory investigation but has seen limited clinical use. It is an electronically actuated device with adjustable rate (0.33–10 Hz), inspiratory time, and pressure. It may be more suitable for prolonged support because, unlike the Paravent Pat, it incorporates a heating and humidification system.

8.2.1.2.2.4 Monsoon Jet Ventilator

The Monsoon jet ventilator (Acutronic Medical Systems AG Hirzel, Switzerland) has been used primarily for ENT surgery and thoracic surgery and has seen limited applications in intensive care for patients with severe lung injury and air leak complications. The ventilator has an integrated humidification and heating system, which is automatically adjusted according to the actual minute volume delivered to each patient, making it potentially suitable for extended use. It is capable of frequencies of 0.2–10 Hz, % inspiratory time 20–70 %, PEEP 10–40 cm H_2O and uses driving pressure of 0.4–3.5 bar. No systematic evaluation of safety and effectiveness is available.

8.2.1.2.3 Performance Characteristics of HFJ Ventilators

There are limited data on the performance characteristics of modern jet ventilators. Boros et al. compared the Bunnell Life Pulse jet ventilator to the Gould HFOV device (forerunner of the SensorMedics) in cats with normal lungs and found that equivalent gas exchange was accomplished with much lower peak and mean pressures with HFJV, and at equivalent airway pressures there was more efficient CO_2 elimination (Boros et al. 1989). Fredberg et al. compared eight different HFV devices, including the Bunnell Life Pulse, using a test lung (Fredberg et al. 1987). They found that the HFJV V_T increased at higher frequencies, in contrast to most other devices, where the V_T fell with increasing frequency. HFJV V_T delivery was more affected by lung compliance, in contrast to the oscillatory devices. These findings are contrary to what might be expected with a fixed inspiratory time, and

more recent *in vitro* studies suggest that V_T actually decreases with increasing frequency of the Life Pulse at any given inspiratory time, likely due to the increase opposing impedance arising from the exhaled gas stream at higher frequencies (Prof J. Pillow, 2010). Similarly, whereas V_T delivery during HFJV is highly dependent on compliance, when compliance is low, the threshold compliance (reflecting the point at which there is minimal additional change in V_T with increasing compliance) is independent of frequency during HFJV (Prof. J. Pillow, unpublished data), presenting a stark contrast to HFO ventilators such as the SM 3100A (Pillow 2001). All ventilators delivered larger V_T with increased endotracheal tube size. HFJV required the highest proximal pressure owing to the extremely short inspiratory time. Bancalari et al. documented more air trapping with HFJV, compared to HFOV (Bancalari et al. 1987). However, this study was not an optimal comparison as the devices were tested at frequencies of 10 and 15 Hz, well above the optimal frequency range of the jet ventilator. Theoretically, at least, gas trapping with HFJV is critically dependent on the balance between inertive, resistive, and elastic forces within the lung. Of the existing jet ventilators, only the Bunnell Life Pulse ventilator has been subjected to clinical evaluation (Keszler 1991, 1997; Wiswell 1996). The Paravent, Chirajet, and Monsoon devices have not been subjected to systematic clinical evaluation, and therefore, it is not possible to formulate meaningful conclusions regarding their safety and effectiveness.

8.2.1.2.4 HFJV: Technical Limitations and Ongoing Developments

The need for tandem conventional ventilator is more of an inconvenience than a technical limitation. While more cumbersome than a single device, it makes changing to and from HFV to conventional ventilation very easy. The technical limitation of most high-frequency ventilators, including the Bunnell Life Pulse, is the lack of tidal volume monitoring that is now routine with conventional ventilators. Although technically

feasible, continuous tidal volume measurement is not incorporated into the ventilator, and this is a significant potential limitation, given the geometric relationship between tidal volume and CO_2 elimination that is responsible for the ease with which inadvertent hyperventilation can occur. The passive exhalation used with HFJV is considered a technical limitation by some. It should rather be simply seen as a specific characteristic that may have advantages in infants prone to airway collapse where the active exhalation of oscillatory ventilation may be counterproductive. The passive exhalation does result in a modestly lower optimal frequency range for HFJV, compared to HFOV.

A new Whisper Jet patient box has recently been introduced to reduce the noise associated with the pinch-valve action. The new box brings the noise level to around 40 dB, well within acceptable limits and substantially below earlier versions. As part of the process of obtaining regulatory clearance in the European Union countries and elsewhere, which is currently underway, the device has also been updated with a more current microprocessor, internal battery, and a smaller, lighter, lower profile box. These developments should pave the way for wider availability of this device throughout the world and increase its utility during transport (Mainali et al. 2007).

8.2.1.3 High-Frequency Flow Interrupters

High-frequency flow interrupters (HFFI) deliver pulses of fresh gas down the endotracheal tube with only a positive pressure deflection and passive exhalation. Unlike jet ventilators, gas flow in HFFI devices does not pass through a narrow injector cannula. The difficulty is that some high-frequency interrupters have a small negative pressure deflection that straddles the definition of HFFI and HFOV. The Infant Star ventilator was the chief example of that phenomenon. Although the device is no longer manufactured or supported, it is still in use in many parts of the world, especially in the developing countries. Other HFFI devices include the Bronchotron and the Volumetric Diffusive Respirator.

8.2.1.3.1 HFFI: Principles of Gas Exchange

A detailed appraisal of the principles of gas exchange during HFFI has not been undertaken. However, the general principles of gas exchange during HFFI straddle the concepts covered for both HFOV and HFJV in that mean airway pressure controls oxygenation, and carbon dioxide removal is proportional to $f \cdot V_T^2$. The passive expiratory phase demands utilization of lower frequencies than in HFOV to facilitate completion of the expiratory phase and avoidance of inadvertent PEEP.

8.2.1.3.2 Contemporary HFFI Ventilators

8.2.1.3.2.1 Infant Star 950

For many years, the Infant Star 950 (IS950) (Infrasonics, San Diego, USA) ventilator, a high-frequency flow interrupter combined with a conventional ventilator, was widely used in the USA, Europe, and elsewhere. By briefly opening the solenoid proportioning valves, the device generates pulses of fresh gas in the inspiratory limb of the circuit at a frequency ranging from 2 to 22 Hz (usual range 6–15 Hz) and adjustable pressure amplitude. The inspiratory time is fixed at 18 ms. Consequently, the inspiratory to expiratory time ratio ranges from 1: 8 at 6 Hz to 1: 3 at 15 Hz. A venturi placed at the exhalation valve assists the return of pressures to expiratory baseline and results in a modest negative deflection. However, exhalation is largely passive and inadvertent gas trapping is not completely avoided by this method, judging by the increased incidence of air leak complications (Craft et al. 2003; Thome et al. 1999).

8.2.1.3.2.2 Bronchotron

The Bronchotron (Percussionaire, Sandpoint, ID) is a pneumatically powered high-frequency flow interrupter, also referred to as percussive ventilator (HFPV) developed in the 1980s by Dr. Forrest Bird. It is increasingly accepted as a neonatal transport ventilator because of its light weight, ability to function as both conventional and high-frequency ventilator, and relatively low gas consumption. The ventilator has an internal pneumatic timing device which cycles high-pressure gas flow at a frequency of 3–10 Hz. Rate and amplitude are continuously adjustable while

the inspiratory time is not, being determined by the frequency and the mechanical properties of the lungs. The high-frequency gas pulses enter a sliding piston mechanism called a Phasitron through a venturi cavity in its central axis. The Phasitron creates an oscillatory waveform by the rapid movement of a spring mechanism that balances inspiratory and expiratory pressures within preset pressures for PEEP or $\bar{P}_{aw}$. The Phasitron acts as both an inspiratory and expiratory valve. In the inspiratory phase, the pulse of gas is augmented by entrained gas proportional to the pressure difference before and after the venturi. During expiration, the piston springs back opening an exhalation port, and gas is allowed to exit the patient through an adjustable resistor that provides PEEP and regulates mean airway pressure. The mean airway pressure, frequency, and flow (which adjust the gas flow to the Phasitron and control the pulse amplitude) are continuously adjustable.

The main limitation of the Bronchotron is the lack of actual values for the ventilator variables – all dials are marked with values of 1–10, but these numbers do not readily translate to values to which a clinician can relate. Adjustments are made by clinical observation of chest movement and patient response. Frequency is displayed as inflation/min (not Hz) and mean airway pressure can be measured intermittently by flipping a toggle switch changing the phasic pressure display to an integrated mean. The phasic pressure displayed by the rapidly oscillating needle of a mechanical gauge is difficult to read. The other major concern is a lack of alarms or other safety features.

There are limited published data to support the safety and efficacy of the Bronchotron, which was approved by the US Food and Drug Administration (FDA) based on its substantial equivalence to a device in existence prior to the effective date of the law (1979). In a study comparing the SensorMedics 3100A and the Bronchotron in saline lavaged newborn piglets, similar oxygenation and ventilation were achieved, when the devices were adjusted to deliver identical V_T at same mean airway pressure and frequency, but a higher pressure amplitude was needed with the Bronchotron (Messier et al. 2009).

One center recently reported their experience of 134 infants in whom 96 % were successfully transported using HFPV with improvement in oxygenation, ventilation, and acid–base status during the time that the patients were on the transport ventilator (Honey et al. 2007).

8.2.1.3.2.3 Volumetric Diffusive Respirator

The Volumetric Diffusive Respirator – VDR 4 (Percussionaire Corp, Sandpoint, ID) – is a time-cycled, pressure-limited, pneumatically driven high-frequency flow interrupter ventilator similar to the Bronchotron, but more complex and designed for hospital use. The device delivers gas from a pressurized source (25–65 psi) through a pneumatic timing cartridge system. The source gas is interrupted to produce a pulsatile flow which enters the breathing circuit via the Phasitron. Warmed, humidified gas is entrained to augment tidal volume. Tidal volume delivery is determined by flow velocity, inspiratory duration, and supplementary gas entrainment. The VDR 4 is composed of two ventilator systems: conventional and high frequency. The conventional component can deliver up to 70 inflations per minute with independent control of inspiratory time and pressure. The high-frequency component allows programming of frequencies from 0.5 to 30 Hz and amplitudes from 0 to 100 cm H₂O and inspiratory to expiratory time ratio from 1:1 to 1:5. A variety of conventional and high-frequency combinations can be selected. Like the Bronchotron, the VDR was approved by the FDA without requiring proof of safety and efficacy.

There are only anecdotal patient series supporting the putative benefits of the device. In one study, 48 pediatric burn patients with failing respiratory status were changed from conventional ventilation to the VDR. Both ventilation and oxygenation were significantly improved with $PaCO_2$ decreasing from 47 ± 3 mmHg to 39 ± 11 mmHg and PaO_2 increasing from 105 ± 8 to 171 ± 12 mmHg after transition to VDR while peak inflation pressures (PIP) dropped from 52 ± 2 to 38 ± 2 cm H₂O (Rodeberg et al. 1994). A small randomized, controlled study compared efficacy of percussive ventilation with incentive spirometry in reducing number of days of antibiotic use

in adolescents with neuromuscular disease. A total of 18 patients were enrolled (9 per group). Antibiotic use was significantly higher with incentive spirometry (24/1,000 patient-days) compared with percussive ventilation (0/1,000 patient-days). The incentive spirometry group spent more days hospitalized (4.4/1,000 patient-days versus 0/1,000 patient-days) than the percussive ventilation group and had no episodes of pneumonia or bacterial bronchitis compared with three events in the incentive spirometry group, supporting the hypothesis that percussive ventilation may have benefits in helping to clear secretions (Reardon et al. 2005).

8.2.1.3.3 Performance Characteristics of HFFI Ventilators

The IS950 is the only HFFI that has been subjected to an evaluation of performance characteristics. Like the SM 3100A, the IS950 has a complex waveform with multiple harmonics. However, the IS950+ is less powerful than either the SM 3100A or the Humming V, and tidal volume delivery is more dependent on compliance than the SM 3100A, the Humming V, or the Dräger BL800+ (Pillow et al. 2001). There was little change in tidal volume between 5 and 15 Hz at a constant ventilator-displayed amplitude, although it decreased slightly at higher frequencies. In contrast to the other three ventilators studied, independently measured amplitude increased with increasing frequency, despite maintaining ventilator-displayed amplitude at a constant value.

Conclusions

A large variety of sophisticated high-frequency ventilators are available to clinicians. All of these devices are capable of supporting gas exchange with small V_T and at least short-term improvement in the patient's condition. For HFFI, evidence of safety and efficacy remains very limited. As conventional ventilation has become more sophisticated, any significant advantages of HFV will be more difficult to demonstrate conclusively. The situation is made more difficult by the increased use of noninvasive respiratory support modalities, resulting in fewer ventilated patients available for clinical

trials. Limited evidence of efficacy notwithstanding, there remain clinical situations that warrant a trial of high-frequency ventilation. Intensivists are by nature inclined to actively intervene. In order to optimize the chance of benefiting our patients and minimize the risk of adverse consequences, a thorough understanding of the operating principles of each device, including their limitations, is critical. Frequently, physicians try several different devices with little benefit, when a good understanding of pathophysiology would have allowed them to optimize the strategy used on any given device to greater advantage. Often, it is true that the best device to use is the one you know best!

Essentials to Remember

- Each high-frequency ventilator has its own unique operating characteristics.
- Clinical data on non-piston oscillators and flow interrupters are limited.
- The clinician must be familiar with the high-frequency ventilators available in his or her unit so that the particular machine employed can be utilized optimally for the clinical situation of the patient.

8.2.2 Negative Pressure Ventilation: Physiological Aspects

Francesco Grasso and Brian P. Kavanagh

Educational Aims

- Negative ventilation works by decreasing the intrapleural pressure thereby creating a gradient for air to move into the alveoli.
- In experimental data in ARDS models, negative ventilation may have the capability to better recruit the lungs and create less overdistension.
- Negative ventilation (as spontaneous ventilation) can increase the cardiac output because of an increased right

ventricular filling and may be better tolerated than positive ventilation when right heart preload is critical.

- Negative ventilation increases the left ventricular afterload by increasing the aortic transmural pressure; this can be adverse when the left ventricular function is depressed.
- Full body negative-pressure devices do not affect hemodynamics, but “chest only” devices have similar effects as spontaneous ventilation.

8.2.2.1 Introduction

Positive pressure mechanical ventilation via an endotracheal tube is the conventional gold standard for treatment of acute respiratory failure. While endotracheal intubation may expose the patient to complications such as ventilator-associated pneumonia which in turn may prolong hospital length of stay (Fagon et al. 1993), such problems may be mitigated with noninvasive ventilation (either positive or negative pressure).

Negative pressure ventilation works by exposing the chest and the upper abdomen to subatmospheric pressure, which assists – or results in – inspiration; the negative pressure distends the thoracic cage, causing a decrease in pleural and alveolar pressure, and creates a gradient for inspired air to move into the alveoli.

8.2.2.2 Types of Negative Pressure Ventilation

The important components of a negative pressure ventilator are an airtight chamber to enclose the thorax (or thorax plus abdomen) and a power unit capable of generating negative pressure in the chamber.

There are three basic types of device: the tank, the jacket, and the cuirass. The tank ventilator encloses the whole body up to the neck (Corrado 1996: 9), and a collar is necessary around the neck in order to maintain an airtight seal. Most tank ventilators have portholes and windows which allow observation and access to the patient inside the chamber. The jacket ventilators consist

of a rigid nylon-covered cage which encloses the chest and the upper abdomen (Hill 1986); here, airtight seals are necessary around the neck, the arms, and the abdomen. Finally, the cuirass is a rigid shell positioned over the anterior part of the chest (Corrado and Gorini 2006). The surface area underneath the cuirass – where the negative pressure is applied – is smaller than that of either the jacket or the tank ventilator.

Among the three different devices, the tank ventilators are the most efficient. The tidal volume delivered by any level of applied negative pressure is in the following rank order: tank > jacket > cuirass. Because of greater efficiency among negative-pressure options, the tank ventilator is the method of choice to treat ARF; jackets and cuirasses are more commonly employed for long-term (e.g., home) ventilation (Hill 1986; Shneerson 1991).

Negative pressure ventilation can be provided as two modes: continuous negative extrathoracic ventilation (CNEP), where a constant level of negative end-expiratory pressure is applied in order to prevent end-expiratory alveolar collapse. Alternatively, negative pressure can be applied as cyclic negative ventilation plus CNEP, in which case the ventilator generates subatmospheric pressure cycles (corresponding to inspirations) and maintains a (constant) preset level of CNEP during expiration. Traditionally, negative pressure ventilation is operated in a control mode, thereby providing a set number of respiratory cycles each minute, but reducing the possibility for patient–ventilator interactions (Gorini et al. 2002). Technical improvements over the past few years have centered on triggering ability. For example, temperature-sensing triggers can reliably detect a switch from inspiration to expiration by sensing nasal air flow and are able to provide an improved interface for patient–ventilator interactions, thereby making assisted negative pressure ventilation more comfortable and better tolerated (Gorini et al. 2002).

8.2.2.3 Effects on Transpulmonary Pressure (TPP)

The lungs inflate when the transpulmonary pressure (TPP) is sufficiently increased, and deflate when it is decreased. The pressure applied by a

negative-pressure system is immediately directed to the chest wall, and it is the outward movement of the chest wall that causes the increase in TPP and subsequent lung inflation. The chest wall behaves differently if lifted by external negative pressure versus when pushed from inside by positive pressure. The explanation is unclear but it may be related to rib cage distortion due to application of negative pressure on the costovertebral junction, decreasing the chest wall compliance (Borelli et al. 1998). For this reason a higher absolute level of negative pressure needs to be applied to the chest wall to obtain the same level of inflation when compared with positive pressure (Krumpe et al. 1977; Borelli et al. 1998) (Fig. 8.57).

Different effects on chest wall compliance may result from different types of negative-pressure ventilators. For example, a comparison between a chest device and a tank ventilator (Lockhat et al. 1992) reported a lower thoracic compliance with the chest device, possibly because the chest device requires chest wall pressure (by the rigid shell on the rib cage) to maintain an airtight seal (Borelli et al. 1998).

8.2.2.4 Respiratory Effects

Previous reports have indicated that negative pressure ventilation provides effective gas exchange and increased functional residual capacity (FRC) (Sanyal et al. 1977a, b; Sanyal et al. 1975).

Respiratory mechanics during CNEP were studied in self-ventilating newborns with respiratory distress syndrome (RDS) (Bancalari et al. 1973). The key findings were increased oxygenation, maintenance of PaCO₂ (despite a reduction in minute ventilation), and an increase in the FRC. The increase in oxygenation corresponds indirectly to recruitment of atelectatic regions. The reduction in minute ventilation without a corresponding increase in PaCO₂ indicates that the dead space ventilation was decreased.

A laboratory study of PEEP and CNEP, in a surfactant-depleted animal model of saline-lavaged piglets, compared the two approaches at different steps using the same amount of end-expiratory distending pressure (Easa et al. 1994). At each stage, the transpulmonary pressure was the same between PEEP and CNEP, but the end-expiratory

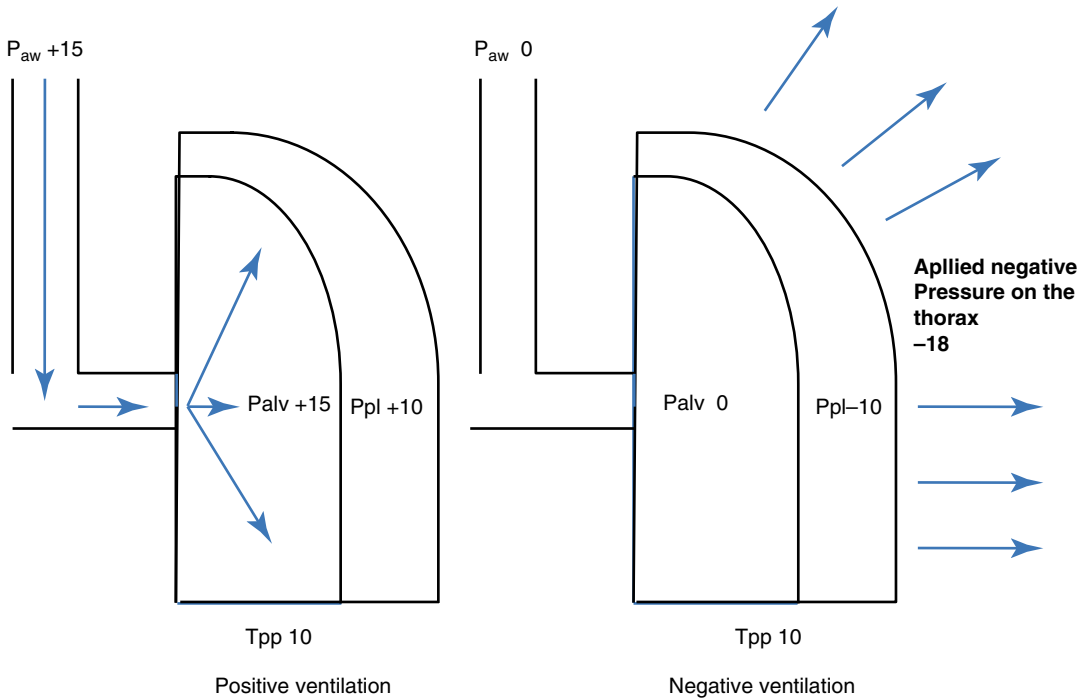


Fig. 8.57 Scheme of the pressure distribution during positive and negative ventilation. In PPV the pressure is transmitted from the airways to the alveoli, and the resultant pleural pressure is positive. In NPV the pressure generated by the ventilator is around the chest and is transmitted to

the pleural space. The airway and the alveolar pressure is always zero. Because of the decreased chest wall compliance during negative ventilation, a higher magnitude of applied pressure is required in order to match the TPP. All the pressure values are in cm H₂O

lung volume (EELV) was higher with CNEP. In a clinical study of adult patients with acute respiratory distress syndrome (ARDS), CNEP was used for matching transpulmonary pressure, and no differences were found in terms of oxygenation or FRC, although CNEP was associated with a reduction in respiratory system compliance secondary to reduced chest wall compliance (Borelli et al. 1998).

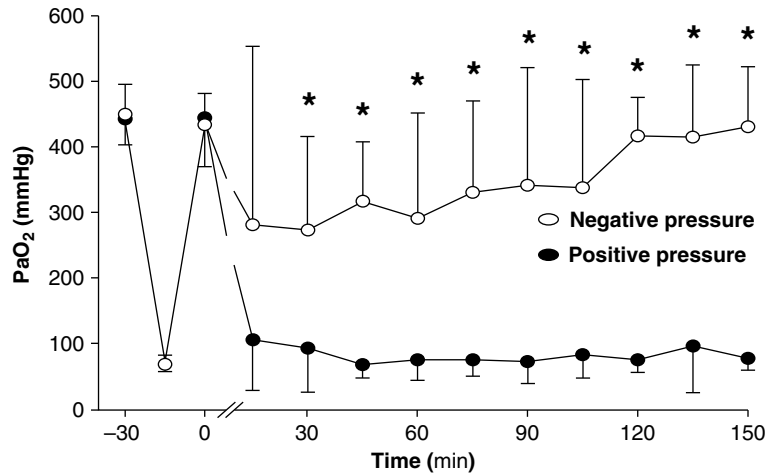
In the studies cited above, negative pressure has been used as end-expiratory distending pressure. A recent study compared volume-controlled ventilation administered via a positive- versus a negative-pressure system in surfactant-depleted rabbits (Grasso et al. 2008). In that study, the absolute amount of end-expiratory pressure was the same in the two strategies, and the peak pressure was adjusted in order to obtain the desired (high) tidal volume. Negative ventilation was associated with better oxygenation which was attributed to superior lung recruitment (and not

to optimized lung perfusion) (Fig. 8.58). These data were supported by CT study of the thorax suggesting less atelectasis during inspiration as well as expiration (Grasso et al. 2008; Helm et al. 2009) (Fig. 8.59). However, precise matching of the pressure-time profile, and especially of the transpulmonary pressure over time, is virtually impossible.

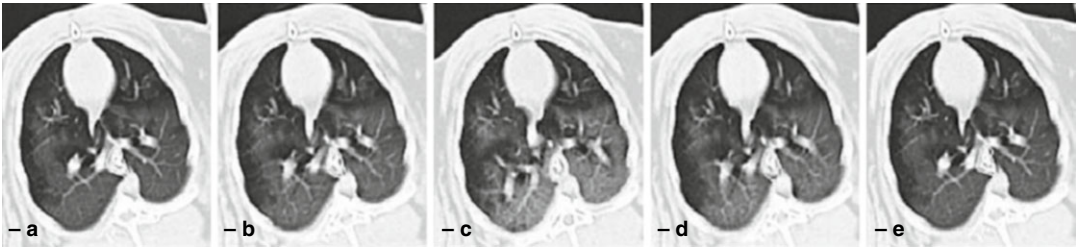
8.2.2.5 Cardiovascular Effects

Spontaneous, as well as controlled, mechanical ventilation induces changes in intrapleural and intrathoracic pressure and in lung volume which can independently affect the key determinants of cardiovascular performance such as ventricular filling (i.e., preload) or the impedance of the ventricle to emptying (i.e., afterload). Such changes in intrathoracic pressure are transmitted to heart, the extrapulmonary large vessels, and the intrapulmonary vasculature. For example, that positive pressure ventilation impedes venous return,

Fig. 8.58 Difference between arterial PO_2 and positive and negative ventilation. Arterial PO_2 was similar in both groups at baseline and during the surfactant depletion process (–30 to time zero). When the two different ventilatory strategies were applied, the PaO_2 was significantly greater in negative versus positive pressure ventilation throughout the remainder of the experiment (* $P < 0.05$) (From Grasso et al. 2008)



Negative



Positive

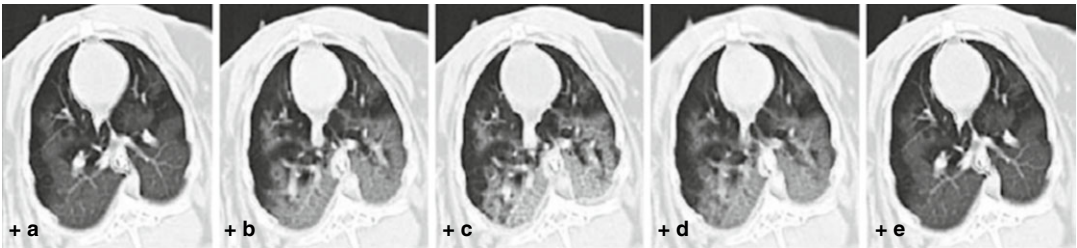


Fig. 8.59 CT comparing positive and negative ventilation at multiple points of the respiratory cycle. Is evident how at end inspiration negative ventilation shows more homogeneous recruitment and less atelectasis at end

expiration when compared with positive ventilation. (a) End inspiration, (b) mid expiration, (c) end expiration, (d) mid inspiration, and (e) end inspiration (From Helm et al. 2009)

thereby reducing cardiac output, has been known for decades (Courmand et al. 1948). The individual elements of cardiovascular performance will be considered below.

Cardiac Output: The cardiac output is the result of a balance among three compartments: the thorax (the pressure in which directly impacts on the pressure in the right atrium); the abdomen (the pressure in which can inhibit venous return and worsen lung compliance); and the peripheral

venous pressure (i.e., closely related to the atmospheric pressure).

The movement of blood from one compartment to another is made possible by the difference in pressure – the “driving pressure” – across each one. The difference between intravascular pressure and intrathoracic pressure (i.e., the pleural pressure) is termed the transmural pressure (P_{tm}). This transmural pressure reflects the pressure in an intrathoracic vessel or in a cardiac chamber

which takes into account the other pressures which are working on that structure. Therefore, for a given compliance, the P_{tm} reflects the effective filling status of the structure in question.

During spontaneous ventilation, the activity of the respiratory muscles on the chest and the diaphragmatic contraction combine to create a negative pressure which enables air flow into the lungs. The same negative pressure is conducted, in the thorax, and increases the P_{tm} . In addition, the venous return from the lower body is enhanced by the transdiaphragmatic driving pressure. These two elements together enhance right ventricular filling, and thereby increase cardiac output. However, pulmonary inflation – even with negative pressure – has an impact on venous return. A study conducted in self-ventilating patients with emphysema (i.e., prone to hyperinflation) described an obstruction of venous return in the inferior vena cava where it enters the thorax during inspiration and normal flow during the expiration (Nakhajavan et al. 1966; 32). The same phenomenon has been described in dogs with normal lungs when extrathoracic negative pressure was applied with very negative values (Wong 1967; 22).

During positive pressure ventilation, the increased intrathoracic pressure is fully transmitted to the right atrium and superior vena cava; this diminishes right heart filling, thereby decreasing cardiac output. Changes in intrathoracic pressure can affect cardiac output by modifying the ventricular afterload: in this context, negative intrathoracic pressures increase the P_{tm} of the ventricles and the ascending aorta (increasing afterload), while positive intrathoracic pressures make it lower (reducing afterload).

Negative pressure ventilation exerts similar effects as spontaneous breathing, but replaces the muscular work by machine (i.e., ventilator) work. However, the hemodynamic effects of negative ventilation depend on the specific mode and timing of application. Ventilation using a chest device (i.e., a cuirass or a jacket) causes hemodynamic effects that closely reflect spontaneous ventilation. However, ventilation with a total body device (e.g., a tank ventilator) results in hemodynamic effects that are comparable to those produced by the PPV; this is because of the

loss of the driving pressure between the abdomen and the right atrium caused by the negative pressure applied to the abdominal surface (Lockhat et al. 1992; Skaburskis et al. 1987).

Left Ventricular Afterload: A standard support for cardiac failure is positive pressure ventilation. PEEP increases the intra-alveolar pressure which mitigates the formation of pulmonary edema; in addition, by increasing the intrathoracic pressure, PEEP also decreases the P_{tm} in the left ventricle (and ascending aorta) and decreases left ventricular afterload. Conversely, negative pressure lowers intra-alveolar pressure, potentially exacerbating the formation of pulmonary edema; and, the increased P_{tm} in the ascending aorta increases left ventricular afterload. For this reason, negative pressure ventilation may be contraindicated in patients with left ventricular dysfunction.

Data from an animal model of heart failure suggest that the cardiac output and the SvO_2 do not change during negative pressure ventilation, but that both are reduced with positive pressure ventilation, especially at high end-expiratory pressures (Skaburskis et al. 1990). The transmural pressure in the left ventricle at the end of diastole tends to be higher with negative pressure, suggesting a higher impact on left ventricular afterload where heart failure may be more severe (Skaburskis et al. 1990). A higher left ventricular end-diastolic P_{tm} corresponds to increased afterload which can worsen ventricular function and potentially lead to hydrostatic pulmonary edema formation. Because NPV can increase the left heart pressures and pulmonary artery occlusion pressure, it can cause hydrostatic pulmonary edema or add a hydrostatic component to preexisting permeability edema. In the latter setting, the edema present in the lung is a consequence of an enhanced inflammatory state, and superimposed increases in pulmonary blood flow (augmented by negative ventilation) could increase extravascular pulmonary water. However, variable results have been found in different studies of lung injury. In oleic acid (Skaburskis et al. 1989) and in bacterial toxin-induced lung injury, positive and negative pressure ventilation resulted in comparable degrees

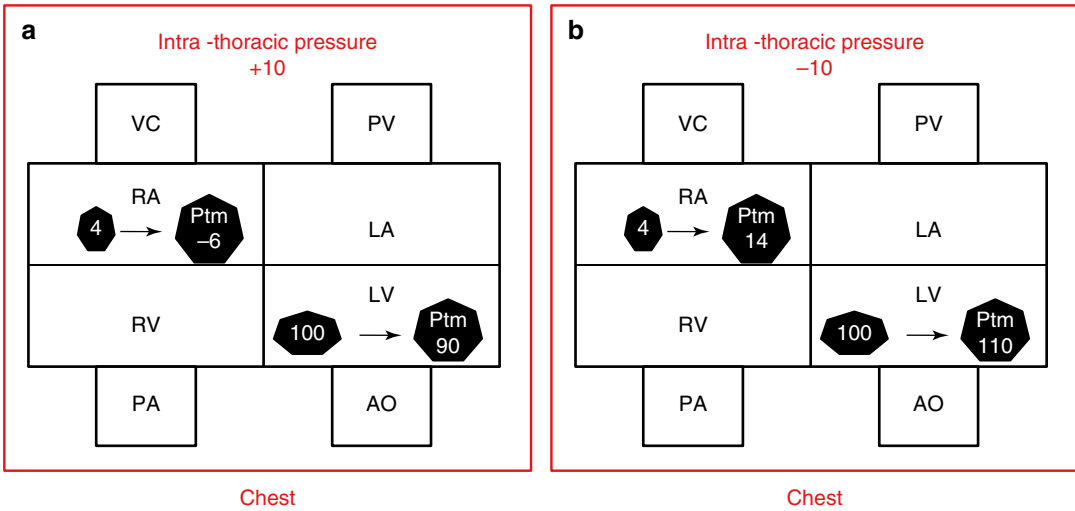


Fig. 8.60 Relationship between intrathoracic pressures and transmural pressures (*P_{tm}*: pressure inside a chamber–pressure outside the same chamber) (*LV* left ventricle, *RV* right ventricle, *RA* right atrium, *LA* left atrium, *PA* pulmonary artery, *AO* aorta, *VC* vena cava, *PV* pulmonary

veins). When the intrathoracic pressure is positive, there is a decrease in the *LV P_{tm}* which leads to a lower afterload; at the right atrial level, the *RA P_{tm}* decreased with consequent decreased preload, when the intrathoracic pressure is negative the situation is opposite

of pulmonary edema (Krumpe and Gorin 1981; Kudoh et al. 1992) (Fig. 8.60).

Pulmonary Vascular Resistance: Pulmonary vascular resistance is the ratio of the pulmonary driving pressures to the pulmonary blood flow (i.e., cardiac output). The cardiac output is the function of preload, afterload, contractility, and lung inflation, as well as ventilation. Lung inflation acts, at least in the experimental isolated lung, on both intra-alveolar and extra-alveolar vessels (Burton and Patel 1958). Where lung volume is close to functional residual capacity, loss of volume results in compression of the extra-alveolar vessels which increases overall resistance. In contrast, when inflated to total lung capacity, increase in volume compresses intra-alveolar microvessels, which is “sandwiched” between the inflated alveoli, contribute to increasing the pulmonary vascular resistance. In this scheme, maintaining optimal lung inflation may be important to minimize pulmonary vascular resistance. Positive and negative (Corrado et al. 1996; 9) pressure ventilation can achieve optimal lung inflation; however, in contrast to negative pressure, positive pressure ventilation may, by reducing right ventricular *P_{tm}*, decrease imped-

ance to ejection and improve pulmonary perfusion. However, experimental studies indicate that the effects on pulmonary vascular resistance are identical with positive and negative pressure ventilation, provided that both systems reference pulmonary vascular pressures in the same way (Mundie et al. 1995).

Essentials to Remember

In conclusion, negative pressure ventilation may have advantages (e.g., better tolerated) over positive pressure ventilation, where the right ventricle is critically preload dependent and where the application is to the chest only; in this context, right-sided venous return is augmented and cardiac output enhanced. In contrast, negative pressure applied to the abdomen retards venous return, and at high levels can increase ventricular *P_{tm}* thereby elevating afterload. While chronic application has many advantages, the acute physiological effects on lung injury and gas exchange are not yet fully understood.

8.2.3 Tracheal Gas Insufflation (TGI)

Claude Danan and Xavier Durrmeyer

Educational Aims

- Understand the rationale for continuous tracheal gas insufflation (CTGI) as an adjunct to conventional mechanical ventilation.
- Learn about physiological effects and mechanical aspects of CTGI.
- Review specific physiological considerations to take in account during conventional mechanical ventilation with and without CTGI in extremely low-birth-weight infants.

8.2.3.1 Introduction

Improving survival of the most immature preterm neonates leads to reaching the limits of conventional ventilation. In that population, for the most severe forms of restrictive respiratory diseases, the high ratio of dead-space to tidal volume (VD/VT) makes efficient CO_2 clearance no longer possible. More exactly, the ventilatory prostheses' dead space is very close to the allowable, in terms of lung protection during mechanical ventilation, tidal volume in neonates (see Sect. 3.4). The CO_2 cleared from the blood at alveolocapillary level stagnates in the anatomic dead space gradually increasing the fraction of inspired CO_2 . CO_2 elimination is thus only possible at the risk of increasing the inspired VT . For the most immature preterm neonates, however, aggressive (i.e., larger VT ventilation) artificial ventilation remains a limiting factor with respect to life expectancy and sequelae-free survival (Meredith et al. 1988; Ambalavanan and Carlo 2006). Under those conditions, we have to consider any technique supposed to be efficient for decreasing or even erasing the anatomic dead space. Shortening of the endotracheal tube is often proposed to limit the prosthetic dead space, but its efficiency is very low because each centimeter of reduced length will

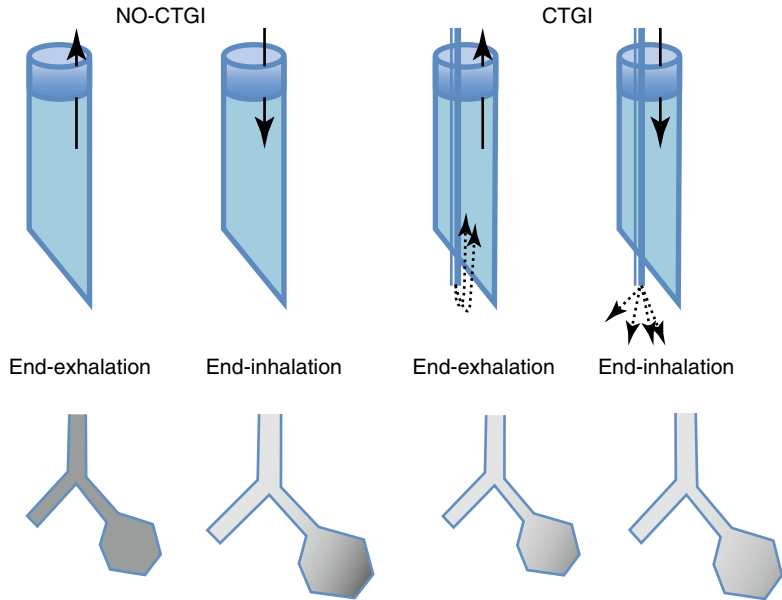
reduce dead space by only about 0.05 mL. As the sum of the different parts that constitute the equipment-related dead space (i.e., 2.5 tube, adapter, Y-piece, and flow sensor or other sensors) is more than 3 mL, a more efficient solution than only trying to cut out a few centimeters of ETT might be required. Furthermore, removal of sensors and shortening tube length may render the baby less comfortable and, in the absence of a flow sensor that allows not only for volume measurements but also for patient–ventilator synchronization, make the respiratory management more difficult. TGI attempts to minimize the negative effect of the anatomic dead space on ventilation efficiency by washing out expiratory CO_2 trapped in the ventilatory prostheses. This technique will be discussed here in different modalities. However, it must be said that at this time no patented device is available on the market. Some animal and human studies confirm the potential benefit of this method that would deserve to be made available for clinical use, which might be the case in the near future, knowing that some commercial development is heading into this direction.

TGI is still seen as a nonconventional mode of mechanical ventilation but should be seen much more as an adjunct to conventional ventilation since it does, conversely to high-frequency ventilation, not modify the physiological basic effects of conventional ventilation.

8.2.3.2 Mechanism of Action

In the conventionally mechanically ventilated patient, CO_2 concentration does increase during expiration in the anatomic and the instrumental dead space. Given the high VD/VT ratio in neonates and in all situations with severe lung restrictive lung pathology (i.e., pathologies with reduced residual aerated lung volumes), most if not all of the CO_2 trapped in the instrumental dead space will be rebreathed during the next inspiratory phase. TGI attempts to minimize this unwanted effect of the instrumental dead space on ventilation efficiency by flushing out actively the CO_2 during the expiratory phase. The method consists in driving an additional flow at

Fig. 8.61 Effect of CTGI on CO_2 removal along respiratory cycles. During mechanical ventilation (*left*), CO_2 (in grey) stagnates in the anatomical and prosthetic dead space and is pushed into the alveoli at each insufflation. Adjunction of CTGI (*right*) removes prosthetic and possibly large airways of CO_2 so that CO_2 -free gas is pushed into the alveoli at each insufflation



the bottom of the trachea. During the expiratory phase, the expiratory valve is open and the CO_2 trapped in the instrumental dead space is flushed out through the expiratory valve. At the end of the expiratory phase, the prostheses are entirely discharged from CO_2 , and the gas volume insufflated during the inspiration phase will be free or almost free of CO_2 , increasing the clearance of CO_2 at the alveolar level. This method suppresses the part of additional ventilatory support required to overcome the negative effect of the instrumental dead space, thereby allowing to adjust better the ventilator settings to the real “requirements” of the patient’s alveolar disease. If we consider the whole ventilatory cycle, continuous tracheal gas insufflation (CTGI) has different effects depending on the phase of the respiratory cycle (Fig. 8.61). During the expiratory phase of the respiratory cycle, CTGI washes out the instrumental dead space and during inspiration CTGI participates to tidal volume. We can imagine another effect of CTGI considering the turbulence generated by the CTGI flow at the tip of the ETT that can enhance gas mixing in regions distal to the exit of the additional flow (somewhat similar, although limited, to what happens during high-frequency ventilation),

thereby contributing to CO_2 removal. This effect is hypothetical, difficult to measure, and clearly marginal if we use low flow rates for CTGI. As we will present in the “lung test” chapter below, the whole system functions as a system without any instrumental dead space. If we consider that instrumental dead space is two to four times greater than the anatomic dead space in extremely low-birth-weight infants (ELBW), we can imagine the tremendous benefit of erasing this additional dead space might have. Dead space washout is therefore the main if not the exclusive effect of TGI.

8.2.3.3 Data from Bench Tests in a Test Lung

The theoretical main effect of TGI is instrumental dead-space washout. To confirm this and to understand the possible effect of CTGI on airway pressures, tidal volume and minute ventilation, and on gas humidification, a neonatal setup (ventilator, circuit, and test lung) has been used to test CTGI flow-related physical and mechanical effects in the respiratory system. Various compliance values were used for these tests. All values were in the range of normal and sick term and preterm newborns.

8.2.3.3.1 Equipment Characteristics: Catheter or Specific Endotracheal Tube?

In preterm neonates the inlet diameter of usual ETT is 2.5 mm. To provide additional flow to wash out the instrumental dead space, the insertion in the lumen of the ETT of a catheter large enough to avoid high-pressure and high-velocity flow would increase the inspiratory and expiratory resistance by significantly reducing the lumen's diameter. With a thinner catheter than 1.5 mm of outlet diameter, there would be an increased risk of tracheal mucosa injury by direct aggression of the high-velocity jet flow. In this case, humidification would be difficult to maintain and an insufficiently humidified flow could become responsible for drying respiratory gases with a substantial risk of favorizing mucus plugging. For these reasons it is advisable to use multichannel ETTs [e.g., 990.05.1024 EPRT, Vygon, 95440 Ecouen, France] with 6 capillaries inlaid in the ETT wall to be used for TGI (Fig. 8.62). The multiplicity of TGI channels reduces the flow at the tip of the channel and reduces the risk for jet-induced mucosal lesions. Proper humidification and heating of inspired gas can be therefore easier assured.

8.2.3.3.2 Calculation of CTGI Flow Rate to Wash Out the Instrumental Dead Space

Given the volume of the sum of each component of the instrumental dead space, it is theoretically possible to calculate the flow [L/min] necessary to wash out totally this volume [mL] during each expiration time [s] [TGI flow rate = $60 \times \text{prosthesis volume (V) (mL)} / (1,000 \times \text{Expiratory time (Texp) (s)}$]. The following table gives the theoretical TGI flow for various expiratory times and different prosthesis's volumes.

Texp/V	2.50 (mL)	3.00 (mL)	3.50 (mL)	4.00 (mL)	4.50 (mL)
0.40 s	0.38 (L/min)	0.45 (L/min)	0.53 (L/min)	0.60 (L/min)	0.68 (L/min)
0.50 s	0.30 (L/min)	0.36 (L/min)	0.42 (L/min)	0.48 (L/min)	0.54 (L/min)
0.60 s	0.25 (L/min)	0.30 (L/min)	0.35 (L/min)	0.40 (L/min)	0.45 (L/min)
0.70 s	0.21 (L/min)	0.26 (L/min)	0.30 (L/min)	0.34 (L/min)	0.39 (L/min)
0.80 s	0.19 (L/min)	0.23 (L/min)	0.26 (L/min)	0.30 (L/min)	0.34 (L/min)

Total efficacy is theoretically reached with less than 0.7 L/min of TGI flow rate and less than 0.5 L/min if the respiratory rate is under 60/min with *I/E* ratio under 1/1

8.2.3.3.3 Effect of CTGI Flow Rate on Intratracheal Pressure Rise and on Upstream Pressure

The increase in distal pressure is due to a momentum transfer mechanism (Slutsky and Menon 1987) created at the continuous-flow exit in the endotracheal tube lumen. Increasing CTGI flow rates (ranging from 0.5 to 2 L/min) while using various endotracheal tubes (Fig. 8.63) leads to a rapid increase in pressures in CTGI circuit (Fig. 8.63a) and in distal pressures (Fig. 8.63b), limiting CTGI at flow rates of maximal 0.5 L/min. It is important to note that the distal pressure created by CTGI is 0.85 cm H₂O for 0.5 L/min and cannot be detected at the Y-piece level. Therefore, the ventilator display cannot display the more distal created pressure by CTGI. Thus, for all test and clinical trials, PEEP has been reduced from previous setting by 1 cm H₂O when switching on CTGI.

8.2.3.3.4 Efficacy of CTGI on PCO₂ Reduction in an Artificial Lung Model

While adjusting in a test lung model with anatomic dead space the PCO₂ to a steady value of 50 mmHg (■) using a continuous CO₂ supply (Fig. 8.63d), the reduction in PCO₂ induced by CTGI can be analyzed (●) and then be compared to a lung model without any dead space (○). In such a model setup, PCO₂ levels could be measured to be equivalent in the TGI model with a CTGI flow of 0.5 L/min to the PCO₂ levels measured in dead-space-free model. Moreover, the reduction in PCO₂ increases when tidal volume decreases.

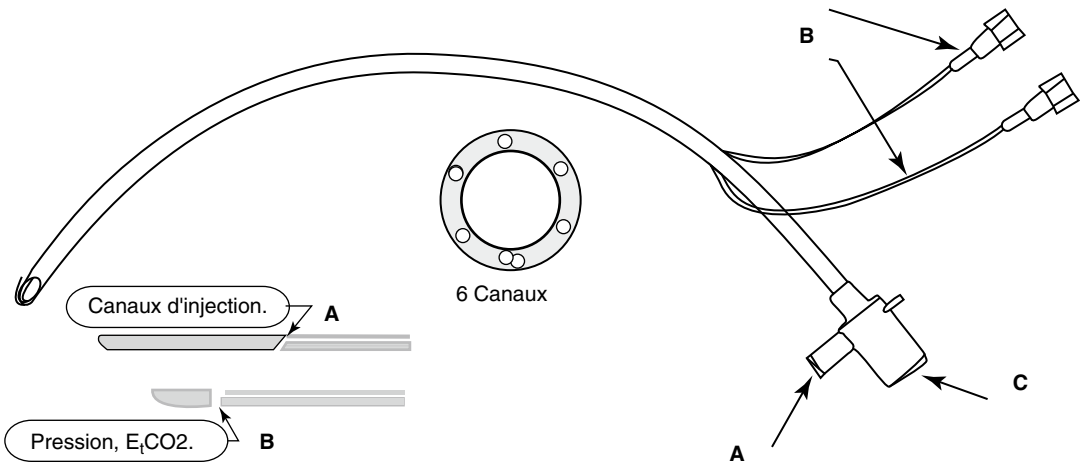


Fig. 8.62 ETT for CTGI. 990.05.1024 EPRT, Vygon endotracheal tube; (A) Six capillaries drive the continuous flow for TGI; (B) two additional capillaries are used for pressure control and surfactant administration; (C) usual connection to the ventilator circuit

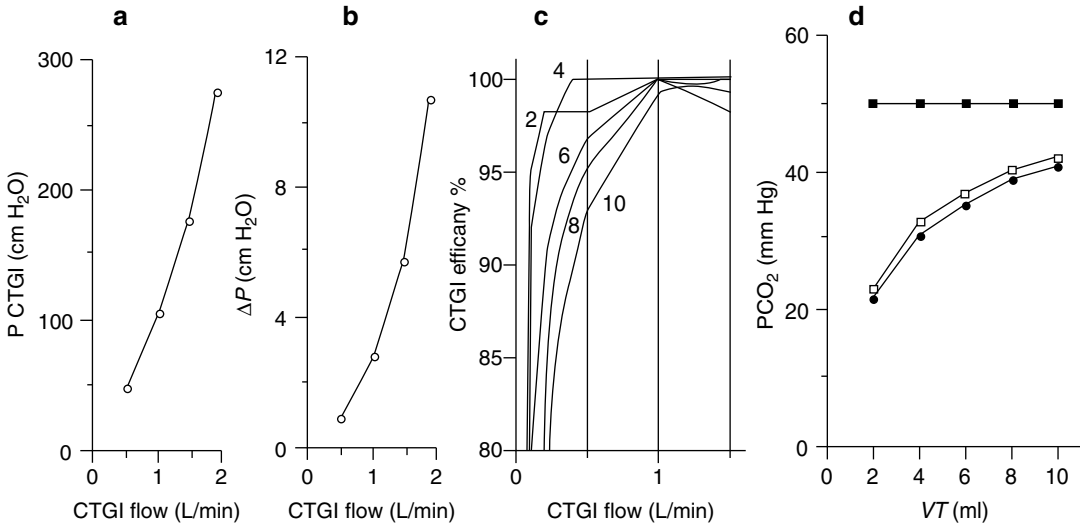


Fig. 8.63 Determination of the optimal CTGI flow rate. (a) CTGI flow is represented on the X-axis. The pressure inside the CTGI circuit is represented on the Y-axis. (b) CTGI flow is represented on the X-axis. The additional pressure generated at the end of the ETT is represented on the Y-axis. (c) Efficacy of CTGI at different flows (X-axis)

and at varying tidal volumes (the number close to each curve denotes the tidal volume used in mL). (d) PCO₂ changes in a CO₂-filled test-lung model during conventional ventilation (full squares), conventional ventilation plus CTGI (full circles), and conventional ventilation in a dead space-free model (empty circles) at various tidal volumes (X-axis)

A 95 % efficacy for CO₂ washout was obtained with 0.5 L/min, over a big range of VTs (2–10 mL) by variation of the TGI flow rate from 0 to 1 L/min for all chosen VTs, with the exception of 10 mL (Fig. 8.63c). For the smallest VT,

95 % of maximal efficacy can even be achieved with a CTGI flow below 0.5 L/min.

In conclusion, for neonates intubated with a 2.5-ETT, a 0.5 L/min TGI flow rate seems to be the most appropriate. It is sufficient to erase

instrumental dead space, but it increases the pressures all along the ETT by 0.85 cm H₂O. If we want to adapt the flow to specific conditions, it is possible to decrease the flow rate according to the smallest tidal volumes (Fig. 8.63c). Otherwise, for a same volume to wash out during expiration time, the longer expiratory time necessitate the lower CTGI flow rate.

8.2.3.4 Physiological Consequences of CTGI

8.2.3.4.1 Effect of CTGI-0.5 on PEEP and ΔP

A key issue is to know whether TGI modifies infant's tidal volumes and/or minute ventilation. While using pressure-limited ventilation provided by a continuous-flow apparatus, as is standard practice in neonatal intensive care units, tidal volume is not set directly but is dependent on mechanical characteristics (compliance and resistance) of the respiratory system (ventilation circuit, infant) and on ventilator settings, i.e., peak inspiratory pressure (PIP) and peak end-expiratory pressure (PEEP) and the difference between these two pressures (ΔP), inspiratory time, and flow. Initiating TGI has no effect on most of these parameters: Respiratory system characteristics, PIP–PEEP difference, inspiratory time, and flow remain unchanged in experimental settings (Dassieu et al. 1998) (Fig. 8.64). The only modification in parameters that can be observed is a slight but consistent increase in mean tracheal pressure distal to the outlets of the TGI capillary tubes. The numerous measurements that we performed on test lung and on patients demonstrated that this increase was consistently ≤ 1 cm H₂O. This increase, however, is not detectable in the ventilator circuit and on therefore the ventilator display cannot indicate it. This pressure increase remains stable during the whole respiratory cycle therefore not influencing the ΔP (i.e., the pressure difference between PIP and PEEP). The absence of CTGI-induced VT or minute ventilation changes is confirmed by direct VT and minute ventilation measurements downstream the ETT, taking into account both main and CTGI flows (Dassieu et al. 1998).

8.2.3.4.2 Contribution of CTGI-0.5 to V_T

To determine relative volume distribution of two gas sources injected in one system, a dilution technique can be used. In that two gases with different oxygen concentration, one for the ventilator ($FiO_2=0.21$) and the other for the CTGI circuit ($FiO_2=1$), have to be used. Determination of the resulting FiO_2 in the test lung allows then calculation of the contribution of CTGI to the delivered V_T as follows: If “A” is the fraction of V_T generated by CTGI, $A=(\text{measured } FiO_2-0.21)/(1-0.21)$. CTGI-0.5 does make an important contribution to VT in all test situations (various VTs over a range of 2–10 mL), ranging from 40 to 100 % (Fig. 8.64a). CTGI contribution increases when tidal volume and breathing rate decreases. Furthermore, it increases with CTGI flow rate but is not sensitive to isolated variation of inspiratory time settings.

8.2.3.4.3 Ventilation Gas, Humidity, and Temperature Tests

The temperature and relative humidity were determined with a thermo-hygrometer (Testo 610, Lenzkirch, Germany) in the test lung under various ventilatory conditions, using conventional mechanical ventilation, ventilation and CTGI-0.5 with CTGI gases derived directly from a wall source, and mechanical ventilation and CTGI-0.5 with CTGI-0.5 derived from the humidified inspiratory gases (MR 730 Fisher and Payckel, Auckland, New Zealand). The test lung was placed in an incubator at 37 °C to simulate the conditions of clinical use. Under test conditions (Fig. 8.64b), CTGI-0.5 with non-humidified unwarmed gases induced a marked decrease in relative humidity and, to a lesser degree, a decrease in the temperature measured in the test lung. With humidified and warmed gases in the CTGI circuit, as described later, relative humidity with IPPV plotted against relative humidity with IPPV+CTGI-0.5 (Fig. 8.64c), the humidity was well preserved ($r=0.92$).

8.2.3.4.4 Continuous-TGI or Intermittent-TGI During the Expiratory Phase?

As it was suggested before, TGI has its major effect in terms of CO₂ washout during expiratory phase, but for different reasons, the additional

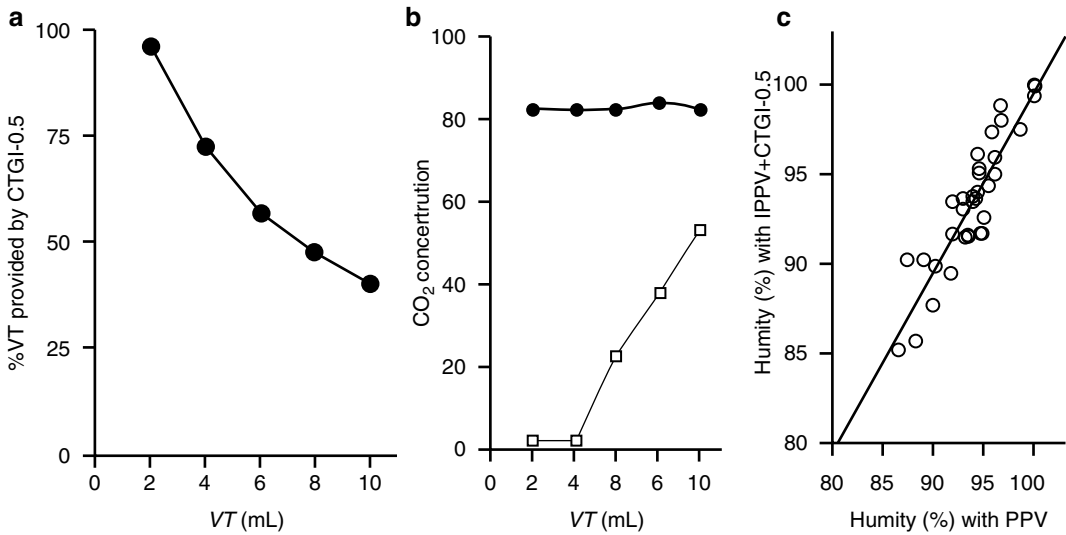
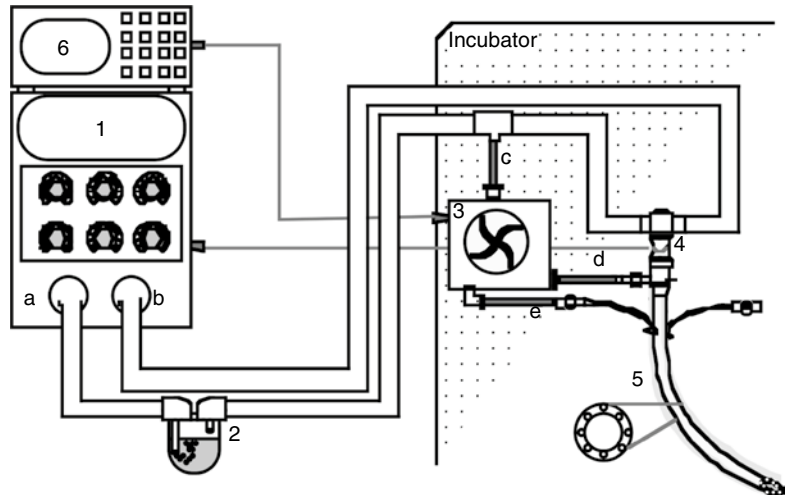


Fig. 8.64 Influence of CTGI on alveolar gases. Contribution of CTGI-0.5 to VT and influence on humidity

Fig. 8.65 Assembly diagram for controlled positive pressure ventilation and CTGI. 1 Ventilator, 2 heater/humidifier, 3 CTGI pump, 4 spirometer holder, 5 endotracheal tube, 6 monitoring and safety module. a Inspiratory circuit, b expiratory circuit, c inlet CTGI circuit, d outlet CTGI circuit, e tracheal pressure transducer



flow is as efficient and easier to achieve if it is continuously blown during both expiratory and inspiratory phases.

8.2.3.4.5 Safety Considerations

As the TGI flow exits at the tip of the ETT, any mucus plug in the ETT forbids unrestricted exhalation, thereby increasing the risk of air trapping even if the ventilator would react correctly to this obstruction by reducing delivered tidal volumes if set in a TCPL mode. Therefore, TGI may be appended to conventional mechanical ventilation only if a security device controls the risk of

inadvertent hyperinflation. One possible answer is illustrated by our CTGI model (Fig. 8.65).

Dead-space washout was ensured by an ancillary flow rate of 0.5 L/min (CTGI-0.5) injected into the lower part of the endotracheal tube through six capillaries extruded in the tube wall (990.05.1024 EPRT, Vygon, 95440 Ecoen, France). Two further independent capillaries were used to monitor pressure changes at the tube extremity or inject surfactant. Pressure monitoring in the CTGI circuit and at the extremity of the tube (AST 142PC, Vanves, France) was designed to prevent hyperinflation. Any abnormal rise in

the CTGI circuit pressure would trigger an alarm and then cut the power supply to the pump. An electrovalve (Kuhnke 65231, Malente, Germany) would then open to shorten the time to return to zero pressure. Independent reference transducers were used to validate the pressure (Meriam Instrument Meri-cal LP 2001, Cleveland, Ohio, USA) and flow-rate determinations (Sierra Instruments 822-13-ov1, Monterey, CA, USA)

8.2.3.5 Animal Studies

Reduction of dead space in cases of respiratory insufficiency has long been a preoccupation. Slutsky et al. developed an animal model using constant endobronchial insufflation under apneic ventilation with positive expiratory pressure. This technique, using very high flow rates (up to 30–60 L/min), enabled normocapnia to be obtained. Efficacy varied as a function of flow rate (Slutsky and Menon 1987; Watson et al. 1986) and catheter positioning (Slutsky and Menon 1987). Using slightly lower flow rates in paralyzed (Slutsky et al. 1985) or partially paralyzed dogs (Long et al. 1988), the efficacy of the method was found to be the same if the catheter was positioned 1 cm above or below the carina trachea. This gave rise to the idea of applying this type of tracheal gas insufflation, concomitantly with mechanical ventilation, and several animal and a few human clinical studies were conducted. Nahum et al. developed an animal model combining conventional mechanical ventilation with tracheal gas insufflation via a catheter positioned above the carina and inserted in parallel with the ETT. These authors showed that the technique decreased PaCO_2 (Nahum et al. 1992a). Efficacy depended on the flow rate used (up to 10 L/min) and was little dependent on catheter positioning. Similarly, the configuration of the end of the catheter (distal versus lateral apertures) did not seem important (Nahum et al. 1992b). The method of insufflation was, however, important. Constant tracheal insufflation was more effective than expiratory insufflation, the latter being more effective than inspiratory insufflation (Burke et al. 1993). In contrast, the use of retrograde insufflation was less effective than anterograde insufflation (Nahum et al.

1993). Using a similar animal model, Snadjer showed that tracheal washout with constant PCO_2 enabled a significant decrease in tidal volume and inspiratory pressures (Sznajder et al. 1989). Jonson obtained the same results with expiratory washout only, using a jet-ventilation tube with a channel included in the ETT wall (Jonson et al. 1990). More recently, Shaffer tested continuous tracheal insufflation, using CTGI appended to conventional ventilation, showing a lung-protective effect based on histological findings after a short duration of CTGI compared to conventional ventilation alone (Miller et al. 2004). Associated to liquid ventilation he showed a synergistic effect on lung protection of the two non-conventional approaches (Zhu et al. 2004). More recently, in a rabbit model of acute lung injury, the same author showed that TGI associated with conventional ventilation decreased ventilatory requirements (PIP, VT, and VD/VT), resulted in more favorable alveolar pulmonary surfactant composition and function and less severity of lung injury than conventional ventilation alone (Zhu et al. 2006).

8.2.3.6 Human Studies

At the end of the 1960s, Stresemann proposed a method for anatomical dead-space washout in tracheotomized patients under spontaneous ventilation, using an intratracheal catheter (Stresemann et al. 1969). More recently, studies have shown that intratracheal administration of gas enabled a reduction in tidal volume, dead space, and minute ventilation in the same type of patients (Benditt et al. 1993; Hurewitz et al. 1991; Bergofsky and Hurewitz 1989). After the Stresemann pilot study, studies in man remained rare. Marini's group, using the method described above in 8 adults under mechanical ventilation, studied the effect of tracheal washout as a function of flow rate (2, 4, and 6 L/min) and catheter positioning. A 15 % decrease in PaCO_2 was obtained with the high flow rate (6 L/min) and the most distal catheter position (1 cm above the carina) (Ravenscraft et al. 1993). Nakos obtained equivalent results and showed that tracheal washout at constant PaCO_2 enabled a decrease in V_T , peak inspiratory pressure, and mean airway pressure (Nakos et al. 1994).

In children, the only studies have been conducted in patients who could not be weaned from an extracorporeal membrane oxygenator (ECMO). These patients consisted in two newborns presenting with diaphragmatic hernia (Wilson et al. 1993) and a 16-year-old child experiencing an aplastic crisis in a context of sickle-cell anemia (Raszynski et al. 1993). The method used was a technique developed by Kolobow (Muller et al. 1993), in which the entire ventilatory flow rate is administered by a catheter inserted in the ETT. In all three cases, weaning from ECMO was successfully achieved.

8.2.3.7 Specific Insights in Neonates

In neonatology, pressure-limited continuous-flow ventilators are used in the overwhelming majority of patients. The rate of expiratory valve closure can be preset, and the tidal volume is dependent on three adjustable parameters: continuous flow (which determines the pressure increase slope), pressure gradient (PIP–PEEP), and inspiratory time. Each of these parameters can be set individually and has no influence on the other two parameters. Although flows and volumes can be measured, these ventilators do not allow to strictly control tidal volume or minute ventilation. This is an important difference with adult mechanical ventilation and data coming from experimental use of TGI with adult ventilators. The other differences concern the lung and prosthetic volumes in neonates. Physiological dead space is rarely important in preterm newborns, lung pathologies are often restrictive, V_D/V_T ratio is greater than in adults, and instrumental dead space increases this ratio more in the smallest infants than in adults. For all these reasons, TGI is supposed to be more efficient and simpler to understand and to apply in preterm infants than in adults. For other reasons, as the small size of the prosthesis, importance of humidity, and fragility of lung tissues, TGI must be cautiously designed to avoid tracheobronchial mucosa injuries, plugs, and air leaks (Dassieu et al. 1998).

Conclusion

Lung testing enables to understand the very simple incidence of TGI as an adjunct to con-

ventional ventilation. The only one goal is to erase an instrumental dead space incompatible with minimally aggressive ventilation. With pressure-limited ventilation provided by a continuous-flow ventilator, CTGI interferes with conventional ventilation with a slight increment of pressures, easy to correct, without any incidence on minute ventilation. Conversely, gases coming from the TGI flow participate largely to alveolar gases. Subsequently, they have to be precisely enriched with oxygen and optimally heated and humidified. All these considerations, including safety issues, are taken into account in a specific technical assembly proposed in Chap. 22.

Essentials to Remember

High dead space (V_D) to tidal volume (V_T) ratio can limit the efficiency of conventional ventilation especially in extremely low-birth-weight infants in whom V_D/V_T ratio is often greater than in mechanically ventilated adults mainly because of a relative high instrumental dead space. Continuous tracheal gas insufflation (CTGI) appended to pressure-controlled mechanical ventilation aims at removing CO_2 trapped in the instrumental dead space, and by this it allows to reduce tidal volumes during mechanical ventilation below 4–5 mL/kg. However, it must be remembered that the additional gas flow that is best provided through specially designed endotracheal tubes with several very small in-wall channels that allow best to keep correct gas humidity and also reduce the pressure buildup along the neonatal endotracheal tube to less than 1 cm H_2O with TGI flows of 0.5 L/min. Accordingly it is advisable to reduce PEEP settings on the ventilator by 1 cm H_2O when turning on a TGI flow. TGI flow rates of 0.5 L/min seem to be sufficient to compensate in terms of CO_2 washout for the instrumental dead-space effect in the neonatal setting. When using this technique, appropriate safety conditions must be provided.

8.2.4 Liquid Ventilation

Thomas Schaffer

Educational Aims

- To understand the chemical physical properties of perfluorochemical (PFC) liquids
- To understand the concept of liquid ventilation, especially its impact on pulmonary mechanics and gas exchange

8.2.4.1 Chemical Properties

Supporting respiratory function utilizing a liquid to eliminate the liquid–gas interface is a more than 50-year-old concept. Published data from the 1950s and 1960s supported the use of saline as a respiratory medium to accomplish the goals of oxygen delivery and carbon dioxide removal. Mammalian animals have successfully breathed hyperoxygenated saline and returned to air breathing. While these animals were successful in delivering oxygen to hemoglobin, it was noted during experiments that they eventually began to retain carbon dioxide and develop a significant metabolic acidosis. These findings in combination with the detergent-like action of saline in removing pulmonary surfactant led to the abandoning of saline as a liquid breathing medium (Mead et al. 1957; Kylstra et al. 1966, Kylstra 1970, 1974; Shaffer et al. 1976; Shaffer 1987, 2004; Wolfson and Shaffer 1990).

Many other liquid media were investigated as potential alternatives to saline including animal and vegetable oils as well as silicon. None of these alternatives were found to be suitable substitutes

for saline as they demonstrated numerous toxic effects on the pulmonary parenchyma (Shaffer 2004; Clark and Gollan 1966; Clark 1985; Moore and Clark 1985).

Perfluorochemical (PFC) liquids were developed during the Manhattan Project and are unique in many ways. PFC liquids are known to have extreme thermal, chemical, and physical stability. They can be stored at room temperature indefinitely and subjected to antiseptic conditioning without alteration, and they are clear, odorless, non-transformable, and generally insoluble in aqueous media. Table 8.17 describes the chemical properties of the PFC liquids as a general class (Shaffer 2004; Lynch et al. 1983)

They are generally formed through the addition of fluorine to cyclic carbon molecules such as benzene through a variety of chemical synthesis reactions. They can be made through vapor phase fluorination, cobalt trifluoride agitation, or electrochemical fluorination. Fluorine replaces carbon-bound hydrogen and it is these carbon–fluorine bonds that give the PFC liquids their unique characteristics (Sargent and Seffl 1970).

In addition to their remarkable chemical characteristics, the PFC liquids as a class demonstrate remarkable gas solubility characteristics. Oxygen dissolves in PFC liquids approximately 20 times more readily than in saline. The solubility of carbon dioxide, however, is much more variable and dependent upon the specific physical properties of each individual PFC (Shaffer 2004)

While the gas solubility properties of PFC liquids make them ideal candidates as a liquid breathing medium, there are several characteristics that limit their ability in a spontaneous breathing application. As a general class these liquids have high density, viscosity, and diffusion

Table 8.17 Physical properties of various PFC liquids

Perfluorocarbon	Formula	O ₂ solution mL/100 mL (25 °C)	Vapor pressure mmHg (37 °C)	Viscosity cS (25 °C)
PP2	C ₇ F ₁₄	57.2	180	0.88
PFOB	C ₈ F ₁₇ Br	52.7	11	1
PCI	C ₇ F ₁₅ Cl	52.7	48.5	0.82
PFDMA	C ₁₂ F ₁₈	39.4	2.6	4.35
APF-100	C ₈ F ₁₆	42.1	64.6	1.11
APF-145	C ₁₀ F ₂₀	45.3	8.9	1.44
APF-215	C ₁₄ F ₂₆	37	0.2	8

Table 8.18 Ideal properties of a fluid as a respiratory medium

High respiratory gas diffusion coefficient
High respiratory gas solubility
Low density and viscosity
Low vapor pressure
Inertness

coefficients which make the work of breathing during spontaneous respiration significantly greater when compared to gas breathing. In addition these same properties result in longer inspiratory and expiratory times as more time is needed in both phases of the ventilation cycle for the movement of the liquid media.

Table 8.18 presents some of the ideal properties of the fluid for a liquid medium to achieve ventilation (Lynch et al. 1983). There are numerous PFC liquids that can be created by chemical techniques; however, not all are ideally suited to serve as a respiratory medium. Fluids of a higher vapor pressure may evaporate more quickly from the lung than those of a lower vapor pressure. Fluids with a lower spreading coefficient may be more difficult to distribute throughout the lung than those with a higher spreading coefficient. Fluids of a higher density will resist redistribution throughout the lung and offer greater resistance to flow. Finally, the ability of the liquid to dissolve gases and carry large amounts of those gases is crucial in determining the functionality of any liquid's ability as a respiratory medium. All of these factors should be considered when choosing an appropriate liquid PFC (Shaffer 2004).

8.2.4.2 Impact on Lung Mechanics

8.2.4.2.1 Pulmonary Structure and Function

The diseased infant lung often suffers from conditions that limit alveolar recruitment and limit uniform ventilation–perfusion matching. Liquid breathing media offer several benefits to the overall structure and function of the lung. More volume is displaced per unit change in pressure in the fluid-filled lung than in the gas-filled lung. This improvement in overall compliance is exaggerated when surfactant is deficient. The liquid breathing media removes the gas–liquid

interface, thus reducing or eliminating the surface forces that result in the need for higher distending pressure. Also, the fluid-filled lung demonstrates similar vascular and alveolar pressures resulting in more uniformly distended vascular structures and an overall improvement in ventilation–perfusion matching.

8.2.4.2.2 Pulmonary Mechanics

Surface tension of the alveolar–capillary interface created by the interface between two phases, gas and the lung surface, is the force resisting expansion and determines the amount of work required to create additional surface for gas exchange. It is by altering these forces that liquid breathing offers its greatest benefit, reducing the surface forces that increases the work of breathing associated with newborn respiratory distress syndrome. By replacing this gas–liquid interface with a liquid–liquid interface, surface forces are reduced but not completely eliminated at this interfacial barrier. The greatest reduction in surface tension is seen with total liquid ventilation where the lung is insufflated to functional residual capacity and free gases are solubilized. However, improvements are also seen during recovery to gas breathing as well as during partial liquid ventilation. Even during partial liquid ventilation when multiple interfacial barriers are present, compliance is always superior to the gas-filled lung (Fig. 8.66) (Shaffer et al. 1983, 1984, Greenspan et al. 1989; Leach et al. 1996; Tarczy-Hornoch 1994, 1995, 1998). The physical properties of liquid breathing necessarily change the way in which breathing need be accomplished. Because of the increase in density and viscosity of these media, the respiratory cycle while breathing liquid necessarily has to be longer with less frequent cycles per minute. PFC breathing is a process in which inspiratory and expiratory times are prolonged, respiratory rate is reduced, and a lengthened exchange period is necessary for gas exchange to occur (Shaffer 2004).

8.2.4.2.3 Gas Exchange

The ability of any media to facilitate oxygen delivery and carbon dioxide removal is dependent upon the ability of the media to move in and out of the

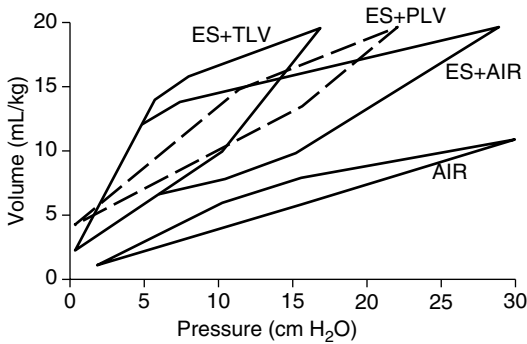


Fig. 8.66 Average pressure–volume curves of excised preterm lamb lung exposed to gas ventilation without (AIR) or with (ES+AIR) surfactant or with perfluorochemical partial liquid ventilation (ES+PLV) or tidal liquid ventilation (ES+TLV) (Reprint from Polin et al. 2004)

lung as well as the ability of the media to dissolve and carry gases. In the healthy condition during which surface tension is low and alveolar recruitment is even, ventilation while breathing a gas is ideal. Gases are significantly less dense and viscous and move in and out of the lung easily while efficiently achieving ventilation. However, in a diseased state where surface tension is high and alveolar recruitment is suboptimal, gas breathing results in diminished gas exchange as alveolar hypoventilation and ventilation–perfusion mismatch diminish the effectiveness of ventilation. It is in this condition that liquid breathing offers significant benefits to gas exchange. While liquids are significantly more dense and viscous, they improve ventilation by improving uniformity of alveolar recruitment and perfusion throughout all regions of the lung, thus essentially eliminating both hypoventilation and ventilation–perfusion mismatching (Shaffer et al. 1984; Wolfson et al. 1996).

8.2.4.3 Cardiovascular Impact

Early studies utilizing PFC as a liquid breathing medium in healthy adult animals reported decreases in cardiac output, oxygen consumption, pH, and an increase in pulmonary vascular resistance. The studies suggested that while gas exchange was possible with PFC, the weight of the liquid in the thorax was compressive to the great vessels of the heart as well for pulmonary vasculature (Matthews et al. 1978;

Lowe et al. 1979; Sivieri et al. 1981; Lowe and Shaffer 1981, 1986). More recently, however, changes in ventilatory management favoring more moderate recruitment strategies with positive end-expiratory pressure (PEEP) in conjunction with PFC ventilation have reported less compromise in cardiopulmonary function (Curtis et al. 1991, 1993; Wolfson 1995). Current studies would support that cardiopulmonary function is minimally impacted by a moderate recruitment strategy (PFC ~10 mL/kg) and that ventilation–perfusion matching is improved.

Essentials to Remember

- Various PFC liquids have various chemical and physical properties, therefore.
- PFC liquids improve ventilation by improving uniformity of alveolar recruitment and perfusion throughout all regions of the lung, thus essentially eliminating both hypoventilation and ventilation–perfusion mismatching.
- The liquid breathing media removes the gas–liquid interface, thus reducing or eliminating the surface forces that result in the need for higher distending pressure.
- PFC breathing is a process in which inspiratory and expiratory times are prolonged, respiratory rate is reduced, and a lengthened exchange period is necessary for gas exchange to occur.

8.3 Noninvasive Positive-Pressure Ventilation in the PICU

Sandrine Essouri

Noninvasive ventilation is now used as a first-line treatment in the management of acute respiratory failure (ARF). Interface choice can strongly influence the efficacy and tolerance of NIV by air leak, facial skin erythema, skin damage, or eye irritation.

The best choice of interface for children patient is a major challenge for pediatricians and requires careful evaluation of the child. The development of new devices specially designed for small patients can minimize these adverse effects when associated with increased use of the NIV.

The nasal mask is widely used for NIV or CPAP most often in ventilation of chronic respiratory failure. During ARF, patients breathed through the mouth to bypass the nasal resistance, but this increase air leaks and can reduce efficacy of NIV. Thus, oronasal masks are preferred for patients with ARF and these masks have the advantage of eliminating significant oral air leaks which should improve the efficacy of NIV. Another new interface, the helmet, should have a real place in PICU to provide NIV. Because of its comfort and good tolerance, the helmet can be used alternately with masks to provide ventilatory support. Education of pediatricians and nurses along with who install the interfaces to maintain a good seal without side effects should be a goal for NIV users.

Progress in development of specific pediatric interfaces has been made but these are still insufficient. The cooperation between physicians and industry should be developed to create adapted interfaces for the newborn to young adult.

Educational Goals

- Precise respiratory physiological characteristic with implications for the choice of interfaces.
- Make a list of available interfaces for NIV in pediatrics.
- Identify the benefits and side effects of each type of interface.
- Enable the practitioner to choose the most relevant interface to optimize the comfort of the child according to the clinical situation.

Noninvasive ventilation is a technique of ventilatory support that does not use an endotracheal interface. Noninvasive ventilation is now used

as a first-line treatment in the management of acute respiratory failure (ARF). Depending on the type of respiratory failure, the child's age, the choice of interface will be an oronasal mask or nasal interface. Interface choice can strongly influence the efficacy and tolerance of NIV by air leak, facial skin erythema, skin damage, or eye irritation.

The best choice of interface for children patient is a major challenge for pediatricians.

8.3.1 Technical Considerations

As its name suggests simplicity, the NIV is in fact a ventilatory assistance requiring specific technical knowledge and experience of practitioners. The increased importance of NIV in pediatric intensive care medicine and the new interfaces for its application led to the development of special modes of intensive care ventilators to overcome the problems related to the type of interface essentially higher air leakage and dead space. Although the basics of the respiratory physiology are similar in adult and older children, major differences do exist, especially between the very young children and adults. Young infants are characterized by a very compliant chest wall that impedes the ability to generate adequate tidal volume and increases the work of breathing by wasting force on chest wall distortion instead of generating effective alveolar ventilation, contributing to muscle fatigue (Davis et al. 1988; Papastamelos et al. 1995). The respiratory system is also hampered by high-flow resistance of the nasal airway and small airway, by hypertrophy of adenoids and tonsil, and by a small zone of apposition of the diaphragm and horizontal ribs; all these physiological properties curtail the endurance of the respiratory system (Devlieger et al. 1991; Hershenson et al. 1990; Openshaw et al. 1984).

NIV is based on the application of a positive pressure (or volume) to the airways and varies with the user effort and the mechanical characteristics of the respiratory system such as compliance, resistance, auto positive end-expiratory pressure, respiratory rate, and potential leakage.

Trigger, usually sensed as flow change in the system, is fundamental to achieve a good patient–ventilator synchrony. In case of small children, inspiratory flow may be insufficient to activate the trigger. This is further complicated by the volume added by the humidifier interposed on the circuit.

The expiratory trigger can be set to inspiratory time or, more often, to a value of inspiratory flow. During pressure-support ventilation (PSV), leaks can hinder achievement of the inspiration termination, thus impeding expiration (Calderini et al. 1999; Mehta and Hill 2001). Air leaks may reduce the efficiency of NIV, increase patient–ventilator asynchrony, and reduce patient tolerance. The management of leakage is therefore a real challenge for the success of the NIV. The management of leaks by applying the mask on the child’s face with high pressure is double edged. While the leakage will be reduced, it may seriously alter the skin tolerance and generate short-term skin damage that will impair the patient’s tolerance to the NIV. Schettino et al. studied air leaks and estimated the pressure required to seal the mask to the skin and prevent leaks (Schettino et al. 2001). With full-face mask or oronasal mask, a level of pressure >2 cm H₂O avoids significant air leaks, whereas with a pressure <2 cm H₂O air leaks become relevant. However, if the mask pressure against the face exceeds the skin capillary pressure, it can impair skin perfusion leading to skin damage (Gregoret et al. 2002; Li et al. 2000; Schonhofer and Sortor-Leger 2002).

8.3.2 Machine–Patient Interfaces

During NIV for acute respiratory failure (ARF), the patient’s comfort may be less important than efficacy, but mask fit and care are needed to prevent air leaks that can reduce efficacy of NIV and skin damage that can decrease patient tolerance.

In the last few years, the industry has made a great effort on interfaces to provide more comfortable, better tolerated, and safer interfaces for adults. In the pediatric population, patient size and anatomy differs dramatically and this piece has a crucial role in NIV. Although great progress in

Table 8.19

Classes of NIV interface	Characteristics
Mouthpiece	Placed between the patients lips and held in place by lip seal
Nasal prongs	Plugs inserted into the nostrils
Nasal mask	Covers the nose but not the mouth
Oronasal mask	Covers the nose and the mouth
Full-face mask	Covers the mouth, nose, and eyes
Helmet	Covers the whole head and the neck without contact with the face

terms of child-friendly interfaces has been made, we are still in a situation where there is a paucity of masks available for pediatric use. The interfaces have included standard commercially masks, ready-to-use models available in various sizes: pediatric and small adult, medium, and large. The interfaces could be also be custom fabricated, molded directly on the patient (McDermott et al. 1989; Tsuboi et al. 1999), but the time required to manufacture the mask does not allow the use of the custom-made mask for critically ill patients in acute respiratory failure (ARF).

Comparative studies on noninvasive interfaces in the pediatric population is absent despite the important role of this piece for NIV.

The classes of NIV interface are resumed in Table 8.19:

Among these interfaces, only full-face masks are not available for pediatric intensive care unit use; if small sizes exist, they could be used with children depending on the etiology of the respiratory failure. During acute respiratory distress in children, decrease of compliance and increase of resistance result in a shallow respiratory pattern with breathing both through the nose and the mouth. In these acute clinical situations, nasal masks and mouthpieces should not be used.

The Table 8.20 summarizes the characteristics of an ideal NIV interface.

8.3.2.1 Nasal Mask

The standard nasal mask is a triangular or cone-shaped clear plastic device with the air seal over the skin formed by a soft cuff. Nasal masks are available in various sizes (pediatric to adult) and from many manufacturers. The nasal mask

Table 8.20 Characteristics of an ideal interface

Characteristics of an ideal noninvasive ventilation interface for pediatric patient.
<i>Ideal interface</i>
Minimal leaks
Minimal dead space
Available in various sizes
Nontraumatic
Lightweight
Good stability and easy to fix
Nonallergenic material
Low resistance to airflow
Low cost
Nondeformable + easy cleaning

exerts pressure over the bridge of the nose to achieve an adequate air seal which may cause erythema and skin irritation. To avoid or reduce these complications, a thin hydrocolloid flap is added which creates an air seal with less mask pressure on the nose. When using nasal masks, transparent models should be preferred to allow easy inspection of the nostrils to ensure that they are not partly or totally occluded due to an inadequate position of the mask. This risk is higher in small children where even a small displacement can alter the delivery of the pressure support. Head gear that holds the mask in place is important for patient comfort, many types of straps assemblies are available, but most manufacturers provide head gear that is designed for use with a particular mask. Depending on the interface, head gear is attached in two or as many five points on the mask, increasing the points of attachment adds stability. The use of chin strap in case of mouth leaks is possible.

The nasal mask is widely used for NIV or CPAP most often in ventilation of chronic respiratory failure. During ARF, patients breathed through the mouth to bypass the nasal resistance but this increases air leaks and can reduce efficacy of NIV. Some authors advocate the use of nasal masks because they produce less anxiety in young children but no studies have compared pediatric nasal masks to oronasal masks in terms of tolerance and efficacy during ARF (Teague 2003). In contrast, many studies describe the successful long-term use of nasal masks for

home ventilation in young children with neuromuscular disease or congenital central hypoventilation syndrome (Guilleminault et al. 1995; Khan et al. 1996; Marcus et al. 1995; Waters et al. 1995).

8.3.2.2 Oronasal Mask

Many commercial masks are formed by two or more pieces of material: the cushion of soft material that forms the seal against the patient's face composed of polyvinyl chloride, polypropylene, silicon, silicon elastomer, or hydrogel and the frame of stiff material which is transparent in most of the mask and composed of polyvinyl chloride, polycarbonate, or thermoplastic. There are 4 types of face-seal cushion: transparent non-inflatable, transparent inflatable, full hydrogel, and full foam.

Oronasal masks are preferred for patients with ARF because they generally breathe through the mouth to bypass nasal resistance (Soo Hoo et al. 1994) and oronasal masks have the advantage of eliminating significant oral air leaks which should improve the efficacy of NIV. In adults, recent engineering advances have improved mask-face seal comfort with added quick-release straps and anti-asphyxia valves to prevent rebreathing in the event of ventilator dysfunction that automatically open to room air when airway pressure falls below 3 cm H₂O. The mask must have a system of fixing to the child's head which is adapted and thus performant. This is a problem for small children for whom the pediatricians are often required to use adult nasal masks in the oronasal position with an inadapted headgear and straps which overlap each other to maintain a stable and correct position of the mask (see Fig. 8.67).

The first concern for the oronasal mask is the higher dead space but, this is not a drawback when the mask is used with a polyvalent ventilator that takes into account all of the compliance of the breathing circuit and has good flow and volume monitoring. Another major concern for the use of oronasal masks in the acute setting is the potential for significant gastric distension and vomiting. However, different clinical experiences show that the systematic use of a gastric tube discharge can, in most cases, avoid these complications.



Fig. 8.67 Oronasal interfaces used in PICU (Respironics)

8.3.2.3 Helmet

It is now well known that air leaks, patient discomfort, and skin breakdown are common problems with face masks which limits the duration and the efficacy of NIV (Mehta and Hill 2001; Mehta et al. 2001). The helmet was originally designed to deliver high oxygen concentrations during hyperbaric therapy (Bellani et al. 2008) and was then introduced as a tool to deliver noninvasive continuous positive airway pressure. Some advantages of using a helmet are as

follows: no need for a seal around the nose and the mouth, an improved tolerability, and the possibility of fitting it to any patient, even the smaller one, regardless of the face contour. The helmet is made of lightweight and transparent biocompatible plastic material joined by means of a rigid ring to a latex-free collar that provides a soft seal around the patient's upper thorax. The helmet is held in place by straps under the patient armpits or layer for an infant. The helmet is fitted with a bidirectional anti-asphyxia valve which opens

automatically when pressure failed. An access port is available to facilitate nursing. The whole apparatus is connected to the ventilator using a conventional respiratory circuit. The two ports of the helmet act as gas inlet/outlets. The transparency of the device allows the children to see and interact with the parents, nurses, and environment (see Fig. 8.68a).

In a physiological study, Patroniti et al. demonstrate, in healthy volunteers, that the CPAP delivered by a helmet is as effective as face mask CPAP, higher inspiratory concentration of CO₂ was decreased with increased flow rates (Patroniti et al. 2003). In recent nonrandomized studies, oxygenation improvements were similar with the face mask and helmet for noninvasive pressure-support ventilation, but tolerance was better with the helmet (Antonelli et al. 2002, 2004). Regarding the work of breathing, the helmet was associated with less inspiratory muscle unloading and with greater patient–ventilator asynchrony in healthy volunteers (Racca et al. 2005). These findings were also described in clinical studies (Chiumello et al. 2003; Patroniti et al. 2003). In a recent physiological study, Vargas et al. confirmed that helmet NPPV was less effective in unloading the inspiratory muscles compared with the face mask when the same ventilator settings were used, but with specific ventilator settings, helmet NIV provided similar reduced effort than face mask (Vargas et al. 2009). Concerning patient–ventilator asynchrony, with specific settings the authors were able to improve the triggering-on delay but not the cycling-off delay with the helmet. The authors suggest that increasing both pressure-support level and positive end-expiratory pressure rate may be useful when providing NIV via a helmet.

In children, only case report (Piastra et al. 2004; Yildizdas et al. 2008) or small clinical studies (Piastra et al. 2004) is available on the helmet for NIV in acute setting. Codazzi et al. described in 15 children with hypoxemic ARF the use of a reduced-size soft helmet, “baby body,” which is worn under the pubic region as a pair of pants (see Fig. 8.68b) (Codazzi et al. 2006). The small size for infants <10 kg has an internal gas volume of about 7 L, and the large size for infants >10 kg an internal gas volume of about

9 L. With this system the treatment was effective in improving oxygenation after 2 h. To avoid a high level of CO₂ rebreathing, high inspiratory flow rates are required, 30 L/mn in children and 40–60 L/mn in adults (Taccone et al. 2004).

In practice, the helmet should have a real place in PICU to provide NIV. Because of its comfort and good tolerance, the helmet can be used alternately with masks to provide ventilatory support. It can only be used in the PICU with intensive care ventilators and high gas flow rates to ensure CO₂ clearance.

8.3.2.4 Mouthpiece

A mouthpiece is commonly used in patients with neuromuscular disease who require daytime ventilation in addition to their nocturnal NPPV. When patients with neuromuscular disease are admitted to the ICU for respiratory failure, this interface may thus be proposed if the patient is able to maintain a seal around the mouthpiece. However, this interface is not suited for young or noncooperative children.

8.3.2.5 Humidification During NIV in Children

To avoid adverse effects of cool and dry gas on the airway epithelium, warming and humidification of the inspired gas is useful. Dryness of the upper airways is a common complaint from users of NIV in adult. The nasal mucosa can lose the capacity to heat and humidify inhaled air and the mucosa progressively dries and releases inflammation mediators (leukotrienes) with an increase vascularity. Humidification of inhaled air can prevent these adverse effects. In children, any retention of secretions in small airways is likely to increase significantly the work of breathing and should be avoided so humidification is essential. Two types of humidification devices are available, heated humidifier and heat and moisture exchanger (HME), and should be used for short-term and long-term NIV in adults. In children, only the heated humidifier should be used for NIV in acute setting because it adds less dead space. HME and heated humidifiers were compared by Jaber et al. and Lellouche et al. and they found similar results: HME was associated with significantly higher PaCO₂, markedly increased inspiratory effort in hypercapnic

Fig. 8.68 (a) Helmet is connected to the ventilator using a conventional respiratory circuit. The two ports of the helmet act as gas inlet/outlets. The transparency of the device allows the children to see and interact with the parents, nurses, and environment. (b) Correct fitting is ensured by straps under the patient armpits or layer for infant (“baby body”)



patients (Jaber et al. 2002; L'Her et al. 2005). Alveolar ventilation was similar for both but with a greater work of breathing with HME than heated humidifier. These two authors conclude that humidification devices can affect some physiological variable. Nava et al. recently recommended, based on physiological and clinical data, heated humidification during NIV for ARF to minimize work of breathing and maximize CO_2 clearance (Nava et al. 2009).

In pediatric acute setting, only heated humidifiers should be used based on adult data and clinical local experiences.

8.3.2.6 Limitations and Adverse Effects of NIV Interfaces

The noninvasive interface is a crucial determinant of the success of NPPV. It is now well known that most of NIV failure is due to technical problems including mask discomfort, leaks,

and skin lesions (Meduri et al. 1996a). Leaks are systematic in the NIV and target zero leakage is not the goal. However, the key is required to define what level of leakage is acceptable and compatible with efficient ventilation.

Among adverse effects skin lesions is a frequent complication ranging from 2 to 23 % (Gregoretti et al. 2002). Skin breakdown occurs at the areas of mask contact even only after few hours of NIV. In most clinical studies and practical experience, masks are fitted tightly in order to reduce air leaks; however, if the mask pressure exceeds the skin capillary pressure and impairs tissue perfusion, this can cause skin damage. The development of skin lesions is more likely to occur on the nasal bridge where the skin lies upon very little subcutaneous tissue on the nasal bone. Children are growing and, in addition to skin lesions, the NIV may have an impact on the growth of the facial bone of the child with facial flattening and maxillary retrusion present in 68 and 37 % of the patients only during chronic NIV and not when NIV is needed for only a few days.

Eye irritation is another problem, related to mask ventilation but less important than skin breakdown (Gregoretti et al. 2002; Meduri et al. 1996a, b).

With the helmet most of the skin injury should be avoided, but this specific interface has specific adverse effects such as axillae skin damage or the noise arising from turbulent flow at the gas inlet. Cavaliere et al. report noise levels in the helmet equal 100 dB, but the presence of a simple heat and moisture exchange filter on the inlet line significantly decrease the subjective noise perception (Costa et al. 2005).

The most important strategy to prevent adverse effects is to avoid an excessively tight fit. Moreover, having multiple interfaces for children and the ability to toggle these interfaces should avoid skin damage by changing the distribution of pressure and friction. In addition, wound-care dressing has also been used to limit skin damage. Table 8.21 resumes the ways to reduce the risk of skin damage during the NIV.

Gastric distension has been described as an adverse effect of NIV more than an adverse effect

Table 8.21 Tips to reduce the risk of skin damage during NIV in children

Proper interface type and size
Rotate various type of interfaces
Proper harness with correct fitting
Skin and mask hygiene
Thin hydrocolloid on pressure points

of the interface; however, the frequency of this complication is exaggerated. Most pediatricians use a nasogastric tube during ARF and during NIV to avoid gastric distension with great effect (Essouri et al. 2005).

Conclusion

Even if the commercial availability of specific pediatric NIV interfaces is increasing, there is no perfect interface for all children in all situations. The choice of the interface requires careful evaluation of the child. The development of new devices specially designed for small patients can minimize these adverse effects when associated with increased use of the NIV.

Future Perspectives

Pressure support was introduced as mechanical ventilator mode in the 1980s. Since that time different technical advances have been introduced to allow patients to breathe spontaneously during PSV, for example, by the introduction of flow triggering. Currently patients breathing on PSV have a high incidence of asynchrony. Future advances have focused on redirecting the site of triggering from a generated at the patient’s airway to one from an EMG signal from the patient’s diaphragm. This signal theoretically has the advantage of decreasing trigger delay and allowing a closed-loop system to adjust the level of support to the strength of this signal.

Essentials to Remember

- The interface is a piece with a fundamental role for the success of NIV; however, specific pediatric interfaces are not commonly available.
- The right choice of the type and size of interface is a guarantee of performance and compliance with NIV.
- Education of pediatricians and nurses along with who install the interfaces to maintain a good seal without side effects should be a goal for NIV users.
- Progress in development of specific pediatric interfaces has been made, but these are still insufficient. The cooperation between physicians and industry should be developed to create adapted interfaces for the newborn to young adult.

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Andreas Schulze

Educational Aims

- To understand physiology and physics of airway humidification
- To review various humidification principles during invasive and noninvasive ventilation

9.1 Physiology of Airway Humidification

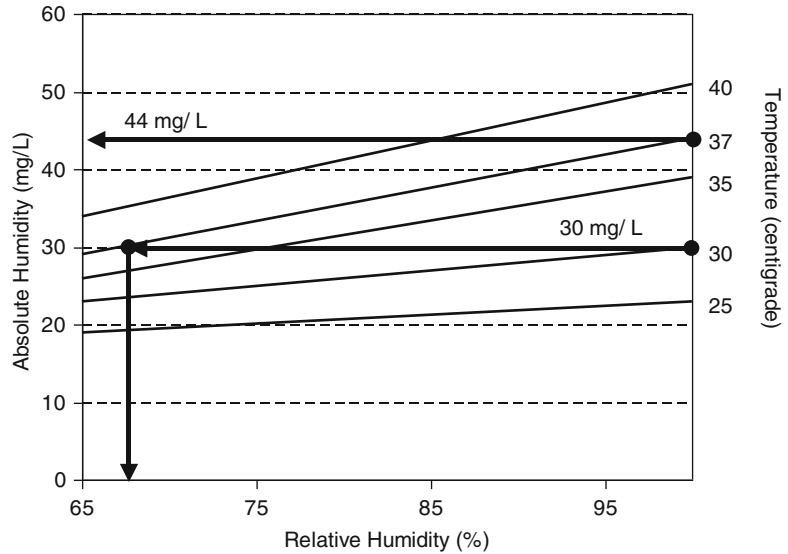
The alveolar air is fully saturated with water vapor at core body temperature while ambient air is cooler and contains less water. This gradient in heat and water vapor pressure is maintained along the nose and upper airways. They function as a counter current heat and moisture exchanger. The inspired air gains heat and water vapor from the upper airway lining which is partly recovered when the expired gas loses heat and water condenses back to the airway surface. This recovery occurs because the upper airway temperature remains below core body temperature during expiration. Breathing is associated with a net heat and water loss because the expired air temperature

is higher than ambient temperature under normal circumstances. The losses must be replenished by the airway epithelium which in turn is supplied by the bronchial circulation. It is unknown under which circumstances the capacity of the airway lining to humidify cold and dry gas becomes overcharged. This capacity is likely different in health and disease. Water transport through the mucosa into the aqueous layer of the airway lining is possibly rate limiting.

The level where the inspired air reaches core body temperature and full saturation with water vapor is called the *isothermic saturation boundary*. It is located at the level of the main stem bronchi in the adult during normal quiet breathing of room air. Its position varies with the heat and moisture content of the inspired air and depends on the pattern of breathing. For example, it will move cephalad with slow and shallow breathing, and oral breathing will move it downwards compared to nasal breathing. Incompletely conditioned air may penetrate deep into the distal parts of the tracheobronchial tree during high minute ventilation of frigid air because of the large volume of air to be conditioned and the short residence time at any given point. Bypassing the upper airway (e.g., by a tracheostomy tube) will also be associated with a much greater burden for humidification on the distal airways. Overall, however, under normal physiologic circumstances, only a small segment of the airway surface is exposed to a temperature below core body temperature and less than full saturation with water vapor.

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Fig. 9.1 The relative humidity of a gas depends on its absolute water content and gas temperature. At 37.0 °C and 100 % relative humidity, the respiratory gas has 44 mg/L absolute water content. If the gas is saturated (100 % relative humidity) at 30.0 °C, its water content will be only 30 mg/L. When the gas is then warmed to 37.0 °C, its relative humidity will fall to below 70 %



9.2 Physics of Humidification

The term “absolute humidity” (AH) is defined as the amount of water vapor (in milligrams) per gas volume (in liters) at a given temperature. “Relative humidity” (RH) is the actual water vapor content of the gas volume (in milligrams) relative to the water vapor content (in milligrams) of this same gas volume at saturation at the same temperature. There is a fixed relationship between AH, RH, and temperature (Fig. 9.1).

Air takes up energy when nebulized water or liquid water is converted into water vapor. Conversely, heat is generated in the process of rainout of water vapor (condensation). Hence, there are two components to the total energy content of air: a sensible and a latent heat content. The air temperature solely reflects the sensible heat while the water vapor mass reflects the latent energy component. It is important to understand that changing the air temperature alone without changes in water vapor mass constitutes a small change in total energy content compared to changing the humidity of the gas. The difference may approach an order of magnitude. Therefore, warming of frigid inspiratory air does little cooling to the upper airway lining compared to the amount of heat loss that incurs when this air is particularly dry. Conversely, if air is inhaled at 39 °C without being fully saturated

with water vapor, it will quickly cool to core body temperature without significant heating of the airway lining. The following illustrates this issue quantitatively in an example: if air is saturated with water vapor at 37 °C in a humidifier chamber and subsequently dry heated to 39 °C in a heated breathing circuit, this dry heating adds almost no energy to the gas—it contains 143 J/g at 37 °C, 100 % relative humidity vs. 145 J/g at 39 °C, 90 % relative humidity. The ASTM humidifier standards state that there is no thermal issue if the gas contains less than 194 J/g of energy. If, however, air enters the airway at much higher than core body temperature and full saturation, there may be a risk of thermal injury to the airway.

There are fundamental differences between nebulized and vaporized water: nebulization creates a dispersion of small droplets of water in air. These particles may vary in size from about 0.5–5 μm . They are visible because they scatter light (clouds) and may carry infectious agents or other particulate matter. In contrast, vaporization generates a molecular, i.e., gaseous distribution of water in air. Hence, water vapor is invisible and unable to carry infectious agents. It will exert a gaseous pressure which amounts to a partial pressure of water of 47 mmHg when air is fully saturated with water vapor at 37 °C. This corresponds to a water

vapor mass of 44 mg of water per liter of gas. The partial pressure of water vapor at saturation depends solely on the temperature. The fraction of water vapor pressure at saturation, 37 °C, and 760 mmHg ambient pressure is therefore $F_{H_2O} = 47 \text{ mmHg} / 760 \text{ mmHg} = 0.062$, i.e., 6.2 %.

9.3 Clinically Relevant Humidification Principles and Devices for Invasive and Noninvasive Ventilation

Medical grade gases have virtually no water content at room temperature. There are three options to deliver water into inspired gas or directly into the airways:

1. Vaporization of water using *heated humidifiers* or *heat and moisture exchangers* (“artificial noses”)
2. Nebulization of water using jet or ultrasonic devices
3. Periodic instillation of bolus water or normal saline solution into the endotracheal or tracheostomy tube as commonly done prior to suctioning procedures

9.3.1 Heated Humidifiers

For various physiological reasons, it is rational to deliver the inspiratory gas at or close to core body temperature and full saturation to endotracheally intubated infants. Heated humidifiers (Fig. 9.2) can achieve this goal. The respiratory gas is warmed inside the humidification chamber to a set target temperature, and water vapor is added from the heated water reservoir. A heated wire inspiratory circuit tubing is then used to maintain or slightly raise the gas temperature so as to prevent water rainout before the gas reaches the infant. At a set humidifier chamber temperature of 37 °C, the gas will absorb a maximum of 44 mg/L of water which corresponds to full saturation (100 % RH) unless the vaporizing capacity of the device is too low relative to the size of the gas flow. The vaporizing capacity of the humidification chamber depends on its water

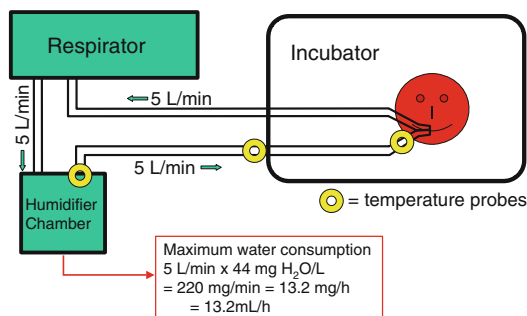


Fig. 9.2 Position of three temperature probes of a heated wire humidification system for infants. The user sets the target temperature to be reached at the endotracheal tube adaptor. This temperature is commonly set at or slightly above 37.0 °C. The temperature inside the humidifier chamber must be high enough to vaporize an amount of water near the absolute water content of gas saturated at 37 °C (44 mg/L). The water consumption rate of a humidifier chamber required to reach a target respiratory gas humidity can be calculated from the circuit flow rate. Observation of this water consumption rate can be employed as a simple test of the efficiency of a humidifier

surface area and on temperature. Recording the water consumption of the chamber over time is a simple test to check for sufficient vaporization. Because most infant ventilators use a continuous constant circuit flow of known size, the absolute and relative humidity delivered at the chamber outlet can be calculated from the humidifier’s water consumption rate. Any decrease in gas temperature along the way from the humidification chamber to the Y adaptor will induce condensation if the gas was saturated at the chamber outlet. This implies that if the chamber temperature was set at or below 37 °C, any rainout in the tubing indicates a moisture loss of the respiratory gas. The gas will then reach the infant underhumidified. It must be emphasized that rainout in the inspiratory limb of the ventilator circuit does not indicate proper humidification in such situations. To the contrary, condensation will necessarily be associated with underhumidification. The inspiratory gas can rapidly cool down in unheated segments of the circuitry. This is promoted by the large outer surface area of small-diameter tubings (particularly when corrugated), by drafts around the tubing (air conditioned rooms), and by a low room temperature. The decrease in temperature will be larger with

smaller circuit gas flow rates due to the longer contact time. Insulating unheated segments of the inspiratory circuit may partly obviate these problems. Rainout should also be avoided for other reasons: condensate gets easily contaminated, may be flushed down the endotracheal tube with risks of airway obstruction and nosocomial pneumonia, and may disturb the function of the respirator. Therefore, in a regular application for an intubated subject, a heated humidifier can be set up with a chamber temperature of 37 °C in order to saturate the gas with 44 mg/L of water. To avoid loss of moisture in the inspiratory limb of the heated circuit, the target gas temperature at the Y adaptor can be set at 39 °C so that the gas arrives with slightly less than full saturation. The gas will quickly cool down to core body temperature inside the adapter and the endotracheal tube.

The technology required for preterm infants is slightly more complex because the ventilator circuit passes through two different environments: the room and the incubator or radiant warmer. The temperature probe close to the patient connection serves to monitor the respiratory gas temperature. It is commonly part of a servo control which aims at maintaining the set gas temperature at the Y adaptor by controlling the heated wire circuit's power output. If the temperature probe is in the presence of a heated field, it may register a temperature higher than the actual respiratory gas temperature as a result of radiation or convection from the warmer environment near the patient. This may signal to the servo to decrease the heating output of the ventilator circuit and lead to loss of gas temperature and rainout. Such problem may arise when the incubator temperature is higher than the targeted gas temperature or from a radiation heat source. Insulating the temperature probe by a light-reflective patch or other material can improve the performance of the system. Another way to alleviate this problem is to place the temperature probe just outside the heated field and use an unheated extension adaptor tubing to carry the gas through the heated field to the infant. The extension tube does not need to incorporate heated wires because its temperature is maintained by the heated field. If cooler incubator

temperatures are employed as usually used for older preterm infants, rainout will occur in the *unheated* segment particularly at low circuit gas flow rates. A circuit should then be used that is equipped with a heated wire along the entire length of its inspiratory limb. Another suitable type of circuit is that with two temperature probes, one outside the heated field and another one close to the Y adaptor. These circuits can perform well over a range of incubator temperatures both above and below the target respiratory gas temperature. This is because the heated wire servo control can be programmed to select the lower of the two recorded temperatures to drive the power output. The maximum heat output of any heated wire circuit may not be sufficient to meet target gas temperatures under extremes of room and incubator temperatures. Also, generic circuits have been on the market that may not be fully compatible with the humidifier and its power source. There has been a warning that covering heated wire circuits with drapes or other material for insulation may involve a risk of melting or charring of circuit components.

9.3.2 Artificial Noses

Heat and moisture exchangers (HMEs) are designed to recover part of the heat and moisture contained in the expired air. A sponge material of low thermal conductivity inside the clear plastic housing of these devices absorbs heat and condenses water vapor during expiration for subsequent release during inspiration. Some HMEs are additionally coated with bacteriostatic substances and equipped with bacterial or viral filters (HMEF). Devices called hygroscopic condenser humidifiers (HCH) use hygroscopic compounds such as CaCl_2 , MgCl_2 , LiCl , or others to increase the water retention capacity.

HMEs may be an alternative to heated humidifiers for several reasons (Dreyfuss et al. 1995):

- Simplification of the ventilator circuit
- Passive operation without requirement of external energy and water sources
- No ventilator circuit condensate
- Low risk of circuit contamination
- Low expense

Small HMEs/HCHs for neonatal applications are commercially available but data on their use is sparse. A pediatric HME maintained an average inspiratory humidity >30 mg/L in a clinical study involving neonates for a test period of 6 h (Schiffmann et al. 1997). Other clinical studies on pediatric and neonatal application confirmed the ability of HMEs/HCHs to conserve heat and to provide humidity levels that are appropriate for short-term conventional mechanical ventilation. Bench studies on high-frequency oscillatory ventilation in a neonatal lung model showed that a neonatal HME was able to provide more than 35 mg/L of mean humidity at the proximal end of the endotracheal tube adapter (Schiffmann et al. 1999). The HME dampened the oscillatory pressure amplitude less than a neonatal endotracheal tube of 3.5 mm ID.

The ability of individual devices to humidify effectively is not reliably reflected by indirect clinical measures such as the occurrence of nosocomial pneumonia, the number of endotracheal tube occlusions, or the number of required tracheal suctionings and instillations. However, visual evaluation of the amount of moisture in the adapter segment between the endotracheal tube and the HME/HCH was found to closely correlate with objective measurements of the delivered humidity (Ricard et al. 1999).

The safety and effectiveness of HME/HCH for *long-term* mechanical ventilation is controversial in adults (Nakagawa et al. 2000) and has not been established in infants. The user should be aware that in specific clinical settings, problems may arise with HMEs from the following:

- Depending on their actual water load, HME add a variable resistance and a dead space to the circuit (Briassoulis et al. 2000; Boots et al. 2006).
- A risk of airway occlusion from clogging with secretions or from a dislodgement of HME internal components has been reported for infants even during short-term application.
- An expiratory air leak will impair the barrier effect against moisture loss. Heat and water escape through an expiratory leak without being recovered by the device.

HME must not be used in conjunction with heated humidifiers, nebulizers, or metered-dose

inhalers. This may cause a hazardous increase in device resistance and/or wash off the hygroscopic coating.

9.3.3 Aerosol Application

Aerosol water particles that range in size from about 1–10 μm may deposit on the airway by impaction (larger particles) or sedimentation (smaller particles). Sedimentation occurs as a gravitational effect when airflow velocity declines in the smaller airways. An aerosol cannot contribute to respiratory gas conditioning downstream the isothermic saturation boundary because the gas is already fully saturated. For this same reason, aerosol water particles cannot be eliminated in this airway region through evaporation and exhalation. They will therefore become a water burden on the mucosa that needs to be absorbed by the airway epithelium. Furthermore, if the aerosol deposition rate exceeds absorption capacity, this may lead to increased airway resistance and possibly narrowing or occlusion of small airways. Severe systemic overhydration subsequent to ultrasound aerosol therapy has been described in a term newborn infant, and similar occurrences were reported in adults.

If an aerosol stream meets the airway proximal to the isothermic saturation boundary, the particulate water can theoretically contribute to the gas conditioning process by evaporation before and after deposition. The droplets, however, contain sensible heat only, and the mucosa needs to supply most of the latent heat for vaporization. This will cool the airway.

Water or normal saline nebulization therefore appears to offer no significant benefit for inspiratory gas conditioning and may entail a risk of overhumidification (Williams 1998).

9.3.4 Irrigation of the Airway

It is common clinical practice to instill small amounts of water, normal saline solution, or a normal saline dilution of sodium bicarbonate into the endotracheal tube prior to suctioning procedures in the belief that this provides

moisture and loosens tenacious secretions. A randomized controlled trial showed a lower endotracheal tube resistance and less hemorrhagic secretions when periodic bolus instillation of normal saline solution was employed prior to suctioning in adults on mechanical ventilation with HMEs. It has been shown, however, that more than 80 % of the instillate may remain inside the airway after suctioning and will probably later be absorbed or removed by the mucociliary system. Suggested amounts of fluid to be used in infants vary widely from 0.1 to 0.5 mL/kg. The safety and effectiveness of this practice under conditions of appropriate warming and humidification of respiratory gases remain dubious.

9.4 Minimum Humidification Requirements

The optimal temperature and humidity of the inspired gas for infants undergoing mechanical ventilation has been a matter of controversy. Also, the minimal acceptable level of temperature and humidity has not been clearly established in clinical studies. There is, however, no doubt that inadequate humidification may lead to progressive airway dysfunction and systemic effects, depending on the degree of underhumidification and coolness, the exposure time, and the underlying disease. It was suggested that humidity levels below a critical threshold of 31 mg H₂O/L are associated with a high risk of endotracheal tube clogging in infants. At least theoretically however, this does not imply that any humidity level above this threshold and below full saturation at core body temperature is safe with regard to airway obstruction. International standards recommend an absolute humidity level of inspired gas >33 mg/L in patients whose supraglottic airway is bypassed (Institute A N S 1997; Miyoshi et al. 2005). This temperature and humidity level can safely be achieved with heated humidifiers over extended periods of time and with currently available brands of artificial noses (HMEs) over several hours during mechanical ventilation.

Essentials to Remember

- Any decrease in gas temperature along the way from the humidification chamber to the Y adaptor will induce condensation, indicating a moisture loss of the previously water-saturated respiratory gas. Therefore, in a regular application for an intubated subject, a heated humidifier can be set up with a chamber temperature of 37 °C in order to saturate the gas with 44 mg/L of water. To avoid loss of moisture in the inspiratory limb of the heated circuit, the target gas temperature at the Y adaptor can be set at 39 °C so that the gas arrives with slightly less than full saturation.
- The temperature probe of a heated humidification system serving to monitor the respiratory gas temperature has to be positioned close to the patient connection. However, when the patient is placed in a heated environment (i.e., incubator), the temperature probe has to be just outside the heated field. An unheated extension adaptor tubing is then needed to carry the gas through the heated field to the infant.
- Despite some drawbacks of artificial noses (HMEs) in the pediatric and neonatal patient, such devices are safe and can provide adequate temperature and humidity levels over several hours during mechanical ventilation.

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Specific Equipment Required for Home Mechanical Ventilation in Children

10

Brigitte Fauroux

Educational Aims

- No ventilator presently available is perfect and is able to adequately ventilate all types of paediatric patients requiring noninvasive positive pressure ventilation (NPPV).
- Numerous ventilators are proposed for paediatric NPPV, but their performances are highly variable and depend on the ventilatory mode, type of trigger and circuit, but, most importantly, the type of patient.
- The inspiratory triggers of most of the ventilators are insufficiently sensitive for infants.
- A systematic paediatric bench and clinical evaluation is recommended before the use of a ventilator in clinical practice.
- Few industrial interfaces are available for children, and this shortage is even more important for infants.
- A systematic paediatric maxillofacial evaluation and follow-up is recommended in children before, during, and after the use of NPPV because of the risk of facial deformity.

Noninvasive positive pressure ventilation (NPPV) may be used in a growing number of conditions and diseases in children, both in the acute and the chronic setting. However, respiratory mechanics and maxillofacial development are different in children as compared to adults, which justify age-adapted ventilators and interfaces. Children requiring NPPV represent a heterogeneous group, not only with regard to the underlying disease but also with regard to age, weight and maxillofacial physiognomy. A paucity of interfaces is available for young children. Individually adapted interfaces may be mandatory for these patients. The ventilators available for home NPPV have been shown to have severe limitations, especially with regard to the detection of the patient's inspiratory effort and their ability to deliver the required volume or pressure within an acceptable time frame for the patient. A close collaboration of the industry with paediatric experts in NPPV should be able to overcome these technical challenges.

10.1 Principles

The aim of noninvasive positive pressure ventilation (NPPV) is to improve or normalise alveolar hypoventilation by means of a ventilator and a noninvasive interface. Both equipments, the ventilator and the interface, should be adapted to the young child, which constitutes a real challenge for the youngest patients. Indeed, breathing pattern differs in children as compared to adults.

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Tidal volume is smaller and respiratory rate is higher in children. In children, normal tidal volume is approximately 10 ml/kg, with a respiratory rate of 40 breaths/min at birth and 20 breaths/min at the age of 2 years. Respiratory failure is associated with a decrease in tidal volume and an increase in respiratory rate. A ventilator should thus be able to deliver small tidal volumes with a relatively high frequency. Also, when a spontaneous mode is used, the ventilator should be able to detect the onset of the patient's inspiratory effort (by means of a change in pressure or flow) and deliver a preset pressure or volume within a time delay compatible with the patient's respiratory rate. As such, trigger time delays exceeding 100 ms for young children are too long and inadequate because the patient may have finished his inspiration before the delivery of the pressure or volume by the ventilator (Fauroux et al. 2008a).

The respiratory effort, i.e. the negative intrathoracic pressure that the patient has to generate during inspiration, varies according to the underlying condition. This inspiratory effort may be extremely high in case of upper airway obstruction or lung disease such as cystic fibrosis (Fauroux et al. 2001a, b, 2004a; Essouri et al. 2005), but very low in case of neuromuscular disease, because of the weakness of the respiratory muscles. It may be difficult for a ventilator to detect the onset of the inspiration in a patient who has a very low inspiratory effort because the change in airway pressure or flow will be too small. NPPV in young children with an "extreme" breathing pattern may thus be very challenging, requiring a ventilator able to detect minor changes in airway pressure or flow and capable of an adapted response within a tight time frame, i.e. 100–150 ms (Fauroux et al. 2001a; Essouri et al. 2005). Such requirements are further challenged by leaks, which are unavoidable during NPPV. Leaks are the main cause of ineffective ventilation with persistent hypercapnia, patient-ventilator dyssynchrony and NPPV failure (Gonzalez et al. 2003). The detrimental effects of leaks are more pronounced in young patients in whom the volume of leaks may represent a greater percentage of the tidal volume. The ratio between the tidal volume and the volume of the

interface is important with regard to rebreathing. Indeed, a large interface, with regard to the patient's tidal volume, will increase the risk of rebreathing.

The anatomy of the facial bones and the proportions between the facial elements are different in children as compared to adults. The anatomy of the maxillofacial structures changes continuously during growth, which is particularly rapid during the two first years of life. Interfaces for NPPV need thus to be adapted specifically to the facial anatomy and physiognomy of children (Fauroux et al. 2005). They need to be changed frequently, especially within the first months of life. Skin injury occurs as a consequence of pressure sores which are defined as a lesion on any skin surface that occurs as a result of pressure. The principal causative factor is the application of localised pressure to an area of skin not adapted to the magnitude and duration of such external forces. Tissue damage will occur if both a critical pressure threshold and a critical time are exceeded. The soft tissue beneath the skin is thinner in children as compared to adults. They are thus at greater risk of skin injury during NPPV. The risk of skin injury is also higher in young children because they need NPPV during extended periods including nocturnal sleep and daytime naps (Fauroux et al. 2005). The repetitive pressure applied by NPPV on the facial structures may hinder the normal development of the facial bones. Facial growth occurs predominantly in an anterior and sagittal axis in children. NPPV hinders this normal facial growth causing facial deformity. Facial flattening and maxilla retrusion are commonly observed in children receiving long-term NPPV and justify a systematic evaluation and follow-up by a paediatric maxillofacial surgeon before and during NPPV (Fauroux et al. 2005).

10.2 Home Ventilators Adapted to Paediatric Needs

Numerous ventilators are proposed for paediatric NPPV, but their performances are highly variable and vary according to the ventilatory mode, type

of trigger and circuit, but, most importantly, the type of patient (Fauroux et al. 2008a, 2004b). Indeed, the same ventilator may be able to correctly ventilate an adolescent with end-stage cystic fibrosis lung disease but not an infant with congenital myopathy.

The choice of the best ventilator for a particular patient is a real challenge for the physician, not so much in the paediatric intensive care unit (PICU) where most of the ventilators have a NPPV mode, as in the home setting. Indeed, home ventilators become more sophisticated and tend to integrate continuously new options and measures. A large number of ventilators are now able to deliver different ventilatory modes, such as PS, with or without positive end-expiratory pressure (PEEP), as well as volume-targeted ventilation. Different circuits (simple, double or leak circuit) and triggers (pressure or flow triggers) may be available on the same ventilator. We have recently shown that the performance of a ventilator may vary according to the ventilatory mode or the type of trigger and circuit but also according to the patient profile (Fauroux et al. 2008a). Indeed, when we evaluated the performance of 17 home ventilators with six different paediatric patient profiles, our conclusions were (1) no ventilator is perfect and was able to adequately ventilate all the six different patient profiles, (2) the performance of the ventilators was very heterogeneous and depended on the type trigger and circuit and, most importantly, on the characteristics of the patient, and (3) the sensitivity of the inspiratory triggers of most of the ventilators was insufficient for infants. A systematic paediatric bench and clinical evaluation is thus recommended before use of a ventilator in clinical practice.

The first ventilators available for home NPPV were either volume- or pressure-targeted devices. Presently, all the home ventilators are able to deliver different, and sometimes combined, ventilatory modes. The simplest devices are pressure-targeted devices that deliver either a continuous positive airway pressure (CPAP) or a bilevel positive airway pressure, i.e. a higher positive pressure during inspiration and a lower positive pressure during expiration. These devices are used with a simple circuit and a leak, generally

inserted in the mask, to allow carbon dioxide (CO_2) clearance. During CPAP, the device should be able to maintain the most constant positive airway pressure during the whole breathing cycle in patients with different diseases or conditions despite changes in respiratory mechanics (such as an increase in airway resistance or a decrease in lung compliance) or leaks. We have shown in a bench study using an adult profile that devices are able to measure the pressure loss in the circuitry and are able to adjust the pressure under dynamic conditions outline the other devices (Louis et al. 2010a). However, these observations have to be validated in the paediatric population. During a bilevel positive pressure ventilation, the ventilator should be able to detect the onset and the termination of the patient's inspiratory effort in order to optimise the synchronisation of the ventilator to the patient. The inspiratory and expiratory triggers of these devices may be fixed or adjustable with generally different levels of sensitivity. The principles and functioning of these triggers is often not very clear and, most importantly, not sufficiently sensitive for young children. Indeed, we have shown that the triggers of these devices are not able to detect the inspiratory effort of infants <18 months of age (Essouri et al. 2005). In these young infants, the use of a bilevel mode was associated with an important patient-ventilator dyssynchrony which resulted in an increase in the work of breathing. In this age group, CPAP is thus preferred to bilevel positive airway pressure. The lack of guarantee of minimal tidal volume or minute ventilation is a limitation of these devices. As such, some recent models have a "volume-guarantee" module, i.e. the possibility to compensate, by increasing the airway pressure and sometimes the inspiratory time, for an insufficient tidal volume. However, we have shown that these modules are not very efficient, especially during air leaks (Fauroux et al. 2010).

Other devices are more sophisticated and are able to deliver a positive pressure or volume with or without a positive airway pressure during expiration. These devices may be used with a simple or a double circuit. In case of a simple circuit, the CO_2 is cleared during the expiration by means of an expiratory valve. This expiratory valve should

Table 10.1 Interfaces for noninvasive positive pressure ventilation in children >8–10 kg

	Nasal mask	Facial mask	Nasal prongs	Mouthpiece
Age	Every age	Every age	Adolescent	Child and adolescent
Contraindications		Gastroesophageal reflux, patient without autonomy		
Advantages	Small volume, comfortable, allows eating and speaking, allows the use of a pacifier in infants	No mouth leaks	No facial contact	Use at libitum (neuromuscular patients)
Limitations	Mouth leaks	Large volume (risk of rebreathing)	Mouth leaks	Ability to seal lips around the mouthpiece (leaks)

have a low resistance to avoid a supplementary expiratory effort (Lofaso et al. 1996). When a spontaneous mode is used, the quality of the inspiratory and expiratory triggers is of major importance. We have shown that the quality of the triggers varies greatly among the different ventilators but also for a specific ventilator, according to the type of circuit, the interface and the patient profile (Fauroux et al. 2008a). Another importance technical requisite is the ability of the ventilator to reach the preset pressure or volume within a time frame and to maintain a constant airway pressure during the whole duration of the inspiration for pressure support (PS) (Fauroux et al. 2008a). This also varies significantly between the different ventilators (Fauroux et al. 2008a, 2004b).

In conclusion, numerous ventilators are proposed for home ventilation in children. In clinical practice, it is recommended to use the simplest ventilator to which the team is familiar, the most important issue being to check the correction of the nocturnal hypoventilation and the adaptation of the patient to the ventilator.

10.3 Machine Patient Interfaces

The interface is a major determinant of the success of NPPV. Different types of industrial interfaces can be used for home NPPV (Table 10.1). Unfortunately, there are no satisfactory interfaces for infants. These patients can thus only be ventilated with custom-made masks.

The choice of the appropriate interface will depend on the ventilatory mode, the age of the patient, his autonomy with regard to the use of the interface, the necessity of daytime ventilation and the skin and facial tolerance. In children, a small interface is preferred because the risk of rebreathing increases with the increase of the interface's size. Moreover, a smaller interface will be less claustrophobic and generally better accepted and tolerated than a larger one. As such, nasal masks are preferred over facial masks. The latter are also strictly forbidden in children who do not have the ability to remove the masks by themselves, such as young children and those with neuromuscular disease, because of the potential risk of inhalation in case of reflux.

Air leaks are the main limitation of NPPV, especially with nasal masks. Leaks are the main cause of persistent hypercapnia (Gonzalez et al. 2003; Paiva et al. 2009). Simple practical measures, such as changing the mask, using a chin strap, increasing minute ventilation and changing the type of the ventilator, may be able to reduce the volume of air leaks and improve the efficacy of ventilation (Gonzalez et al. 2003; Paiva et al. 2009).

Skin erythema or irritation is also a major side effect of the interface (Fauroux et al. 2005). This complication has to be detected and prevented as early as possible by changing the interface or making a custom-made mask. The pressure applied by the interface on the growing facial structures of a child can induce facial deformities. A systematic maxillofacial evaluation

before, during and after the eventual withdrawal of NPPV is mandatory. The interface needs also to be changed frequently in young children, because of their rapid facial growth. It may be recommended to use and alternate different (types of) masks to minimise the risk of skin injury and facial deformity. Systematic humidification of the ventilator gas is not necessary for NPPV because of the respect of the upper airway. However, nasal intolerance due to excessive dryness can resolve after humidification of the ventilator gas. Most importantly, the evaluation of the efficacy of NPPV should consider the “couple” interface + ventilator because the change of the interface or the ventilator may modify the effectiveness of NPPV (Louis et al. 2010b).

10.4 Practical Organisation and Backup Systems

The major advantage of NPPV is that it can be applied at home, combining greater potential for psychosocial development and family function, at lesser cost. The use of home NPPV requires appropriate diagnostic procedures, appropriate titration of the ventilator, cooperative and educated families and a careful, well-organised follow-up. Prior to discharge, the patient's respiratory status should be stable on the actual ventilator and circuit the child will use at home, at least for several days. Settings on a home ventilator do not provide the same ventilation in the child as the same settings on a hospital ventilator, and the efficacy of home equipment must be evaluated in each child prior to discharge. Once the child is at home, and as the child grows, ventilator settings must be evaluated to ensure adequate gas exchange on a regular basis. Although the optimal frequency for these evaluations has not been determined, these evaluations should be performed more frequently in infants and small children because of their rapid growth. Sleep evaluations are recommended as a diagnostic tool before the initiating of NPPV, then as a control test of the efficacy of NPPV before discharge with the ventilator, and as a surveillance test

during an overnight hospital admission during follow-up (Paiva et al. 2009). Careful extrapolation should be made from a sleep evaluation performed during daytime naps because this does not always reflect what happens during the night. Routine and emergency service must be available. Providers/home care equipment technicians and nurses should visit the patient at home at least every month to perform preventive maintenance and check of the interface and the ventilator. Evaluation of compliance should be systematically checked by counters on the equipment determining the amount of time the ventilator is effectively used and not only turned on.

Patients requiring home NPPV may need other supportive therapies. Cough-assisted techniques, by means of the mechanical insufflator-exsufflator, for example, are recommended in every patient with neuromuscular disease who is started on NPPV. The mechanical insufflator-exsufflator is very efficient and well-tolerated in helping the patient clear his respiratory secretions (Fauroux et al. 2008b). Oxygen therapy at home must be justified on the basis of an individual-based medical necessity, as determined by appropriate physiological monitoring, with pulse oximetry monitoring during periods of sleep, wakefulness, feeding and physical activity and arterial blood gases. CO₂ levels should be minimised first by ventilator use before considering oxygen therapy, especially for patients with neuromuscular disorders and obstructive sleep apnoea. It is important to remember that supplemental oxygen is not a replacement for assisted ventilation in patients who hypoventilate.

Children are frequently undernourished when starting NPPV. Chronic respiratory insufficiency is frequently associated with an increase in energy consumption, anorexia and malabsorption. Adequate nutrition is critical for growth and development of the lungs and the chest wall. Nutritional support, via a nasogastric tube, is frequently necessary during the first weeks or months. This can be performed by fashioning a port in a custom-made nasal mask, if gastrostomy feeding is not planned. In infants, discoordination of swallowing mechanisms is frequent, and

swallowing function should be evaluated to assess pulmonary aspiration risks. Many patients have also associated gastroesophageal reflux, which may require surgical correction. This can be combined with a gastrostomy if necessary.

It is essential that the child, if the age permits it, and the parents should have the opportunity to discuss the NPPV therapy in advance. Discussion should start long enough before the anticipated need to allow the child and the family to evaluate options thoroughly and to discuss their feelings. NPPV has here an essential first place as a noninvasive therapy but still represents an objective element reflecting a further step in the severity of a disease. It is crucial to determine short-term and intermediate-term goals of NPPV with the child and the family and to explain the principles of NPPV. A wide range of ventilators and masks are available, and great care will be taken to choose the most appropriate equipment and settings. The final objective is that NPPV translates into well-being and a better quality of life, with a total adherence of the child and his family. In progressive diseases such as some neuromuscular diseases, ventilatory failure may progress at daytime. These patients are generally equipped with a second ventilator. Diurnal NPPV, by means of the patient's usual nocturnal interface or a mouthpiece in older children, may be effective and can delay the discussion for a tracheotomy (Toussaint et al. 2006). However, in some patients, a tracheotomy will become necessary at a certain moment. Close monitoring of the patient's physiological status and disease progression, together with clear information of the family, is essential.

Future Perspectives

- Develop adequate and well-tolerated interfaces for young children.
- Develop home ventilator specifically adapted for young children.
- Develop and validate alternatives to polysomnography for the evaluation of the efficacy of NPPV at home in children.

Essentials to Remember

- No ventilator is perfect and is able to adequately ventilate all the different types of paediatric patients who may justify NPPV.
- The performance of ventilators is very heterogeneous and depends on the type trigger and circuit and, most importantly, on the characteristics of the patient.
- The sensitivity of the inspiratory triggers of most of the ventilators is insufficient for infants.
- The evaluation of the efficacy of NPPV should consider the "couple" interface + ventilator because the change of the interface or the ventilator may modify the effectiveness of NPPV.
- Patients should be regularly and closely monitored after NPPV initiation, to ensure a perfect correction of alveolar hypoventilation and to prevent and detect side effects of NPPV, such as skin injury or facial deformity.

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Part III

Respiratory Mechanics in the Mechanically Ventilated Patient

11.1 Introduction

Mark Heulitt and Katherine C. Clement

Educational Aims

- To review the physiologic aspects of respiratory mechanics on positive pressure ventilation
- To understand the aspects of passive aspects of the respiratory system and its implications on monitoring of respiratory mechanics
- To understand the technical aspects of the measurement of respiratory mechanics and potential limitations and applications

Infants and young children have a number of anatomical reasons and physiological reasons for making accurate measurement of respiratory mechanics in the intensive care unit. Despite advances in the measurement of respiratory mechanics in non-intubated infants, these advances have been slow to be adapted to intubated patients due to technical limitations. Thus, the major role of lung function testing in the ICU has been limited to the research arena. However, despite these limitations it is essential the person caring for the intubated pediatric patient have an in-depth understanding of the respiratory mechanics involved with the use of a positive pressure ventilator.

The same model describing the normal interactions between the airways and the lungs can be applied to the interaction of the mechanical ventilator with the respiratory system. In simple terms, the lung-ventilator unit can be considered as a tube with a balloon network at the end, with the tube representing the ventilator tubing, endotracheal tube and airways, and the balloon network of the alveoli. The movement of gas is determined by forces, displacements, and the rate of change of displacements of the components that are distensible.

In physiology, force is measured as pressure ($\text{pressure} = \text{force}/\text{area}$), displacement is measured as volume ($\text{volume} = \text{area} \times \text{displacement}$), and the relevant rate of change is measured as

flow (e.g., average flow = $(\Delta \text{volume}/\Delta \text{time})$; instantaneous flow = dv/dt ; the derivative of volume with respect to time). The pressure necessary to cause gas flow into the airways and to increase the volume of gas into the airways and to increase the volume of gas in the lungs is the key component in positive pressure mechanical ventilation. The volume of gas (ΔV) to any lung unit (or balloon in simplified example) and the gas flow ($\dot{V}$) are related to the applied pressure ΔP by

$$\Delta P = \frac{\Delta V}{C} + \dot{V} \times R + k$$

where R is the airway resistance and C is the lung compliance. This equation is known as the equation of motion for the respiratory system. The sum of the muscle pressures and the ventilator pressures is the applied pressure to the respiratory system. Muscle pressure represents the pressure generated by the patients to expand the thoracic cage and lungs. In contrast, ventilator pressure is the transrespiratory pressure generated by the ventilator during inspiration. Combinations of these pressures are generated when a patient is breathing on a positive pressure ventilator. For example, when the respiratory muscles are at complete rest, the muscle pressure is 0; therefore, the ventilator must generate all the pressure necessary to deliver the tidal volume and inspiratory flow. The reverse is also true, and there are degrees of support depending upon the amount of force generated by the patient's respiratory muscles. Therefore, the total pressure applied to the respiratory system (P_{RS}) of a ventilated patient is the sum of the pressures generated by the ventilator (measured at the airway) P_{AO} and the pressure developed by the respiratory muscles (P_{MUS}). Therefore,

$$P_{RS} = P_{AO} + P_{MUS} = \frac{V}{C} + \dot{V} \times R + k$$

where P_{RS} is the respiratory system pressure, P_{AO} is the airway pressure, and P_{MUS} is the pressure developed by the respiratory muscle.

11.2 Terminology and Conventions

Main Symbols:

C	Compliance
E	Elastance
f	Frequency
G	Conductance
I	Inertance
PEEP	Positive end-expiratory pressure
P	Pressure
R	Resistance
τ	Time constant (tau)
V	Volume
V_T	Tidal volume
Z	Impedance
$\dot{X}$	Dot above any symbol indicates first time derivative, e.g., $\dot{V}$ is flow of gas

Modifiers:

A	Alveolar
ao	Airway opening
dyn	Dynamic
E	Expiratory
El	Elastic
es	Esophageal
I	Inspiratory
L	Lung
η	Is the viscosity of the gas
p_{aw}	Airway pressure
p_l	Pleural
rs	Respiratory system
st	Static

Examples of Combinations

C_{CW}	Chest wall compliance
C_{dyn}	Dynamic compliance
C_L	Lung compliance
C_{stL}	Static lung compliance
E_{dynrs}	Dynamic elastance of the respiratory system
P_A	Alveolar pressure
P_{AO}	Pressure at airway opening
P_{bs}	Pressure at the body surface (atmospheric pressure)

PEEP _i	Intrinsic PEEP
P _{ES}	Esophageal pressure
P _{plat}	Plateau pressure
P _{pL}	Pleural pressure
P _{RS}	Pressure respiratory system
R _{aw}	Airway resistance
R _{dyn}	Dynamic resistance
R _{ti}	Lung tissue resistance
$\dot{V}_{max}$	Flow max

11.3 Mechanical Model of the Passive Respiratory System

A model of the respiratory system is considered passive because the lungs respond to forces external to the lungs. The respiratory muscles generate these forces in a patient breathing spontaneously. In contrast, during positive pressure mechanical ventilation, the movement of gases is in response to a pressure gradient that is developed between the airway and the environment. However, in both cases it is the physical impedance of the respiratory system that determines the pattern of response of the lung. Generally the major causes of the impedance can be categorized into either the forces related to the (1) elastic resistance of tissue and alveolar gas/liquid interface and (2) frictional resistance to gas flow. Under static conditions when no gas is flowing, it is the elastic resistance to gas flow that governs the relationship between pressure and lung volume. Minor causes of impedance include the inertia of gas and tissue and the friction of tissue deformation.

It has been recognized that the elastic recoil of the lung is not isolated to the stretching fibers of the lung parenchyma but to the combination of these fibers plus the surface tension acting throughout the vast air/water interface lining the alveoli.

Elastic resistance is only one component of the total impedance to gas flow; a much greater part of the residual forms of impedance are provided by what can be categorized as “nonelastic resistance” provided by resistance to airflow and tissue deformation. These can be categorized as

pulmonary resistance and are related to gas flow rate.

In a passive system, the extent of lung inflation reflects a balance between the elastic recoils of the lungs and chest wall, gravitational force, and tension in the respiratory muscles. In this system, when movement occurs, the equilibrium is disturbed and the rate of movement is influenced by the strength of the applied force and by the elasticity, resistance to movement, and the inertia of the thoracic cage, lung tissue, and gas contained in the lung.

Thus, the force applied to a body is met by an opposing force of equal magnitude and is related to the elasticity, resistance, and inertia of the system.

The elasticity of the system can be expressed as elastance which is the reciprocal of compliance (C) and is related to the volume (V), resistance (R), velocity of gas flow, and the inertia (I) to acceleration. All these variables influence the pressure difference across the lung. These can be expressed in Newton's third law of motion:

$$P = \left(\frac{1}{C} \right) V + \left(R \frac{dV}{dt} + I \frac{d^2V}{dt^2} \right)$$

This equation states that a force applied to a body is met by an opposing force of equal magnitude and that this latter force has components related to elasticity, resistance, and inertia.

The necessary force generated to overcome the resistance to movement of the lungs and thorax represents a large energy expenditure and consumption of oxygen. Thus, it is usually the frictional resistance of the lungs and chest wall that limit exercise and the maximal rate that air can move in and out of the lungs. The resistance can be further subdivided into thoracic resistance, pulmonary resistance, lung tissue resistance, and airway resistance.

Inertia according to the laws of physics, force (F) equals mass (M) times acceleration ($G = du/dt$, where u is the velocity of the gas molecules). Pressure is F/A , where A is the area the force is acting on. The mass of a column of gas is $L \times A \times \rho$ where L is the length of the column, A its

cross-sectional area, and ρ the gas density. From this it follows that

$$P = \frac{F}{A} = (L \times A \times \rho) \times G = L \times \rho \times \frac{du}{dt}$$

However, $u = V/A$, and $du/dt = (1/A) \times dV/dt$ where V is the volumetric gas flow. dV/dt is the volume acceleration, which is the same as d^2V/dt^2 , where V is volume. From this it follows that

$$P = \left(\frac{L \times \rho}{A} \right) \times \frac{d^2V}{dt^2}$$

The inertance I therefore equals $L \times \rho / A$. The pressure drop due to inertance is greatest when the flow increases rapidly, as occurs if the frequency of breathing rises. The work performed to achieve the acceleration is stored in the lung as kinetic energy.

Inertial forces are of negligible magnitude except when a high-frequency oscillation is applied for purposes of assisting ventilation or for investigating the mechanical characteristics of the lung.

The forces necessary to overcome the resistance to movement of the lungs and thorax are relatively large and when ventilation is increased requires large energy expenditure and oxygen consumption. Thus, the maximal rate at which air can move into and out of the lungs can be limited. Resistance can be subdivided according to tissue involved including total thoracic resistance, total pulmonary resistance, lung tissue resistance, and airway resistance.

Total thoracic resistance is the sum of the components attributable to the rib cage, the diaphragm, the abdominal wall and contents, the lung tissue, and the gas in the lung and airways. These effects are additive; thus,

$$P_{\text{total}} = P_{\text{th}} + P_{\text{ti}} + P_{\text{aw}}$$

where P is the force required to overcome the frictional resistance and th, ti, aw refer, respectively, to the thoracic rib cage and diaphragm, the

lung tissue, and the lung airways. For the thoracic cage the force is a simple function of the velocity of linear movement. The velocity cannot be measured directly but can be described approximately in terms of the rate of airflow. Then, as a first approximation

$$P_{\text{th}} = R_{\text{th}} \times \dot{V}^{n1}$$

where R_{th} is the resistance of the thoracic cage, in kPa (or cm H₂O) l⁻¹s, and $\dot{V}$ is the airflow (l s⁻¹). In most instances the value of the exponent $n1$ lies between 1.0 and 1.1; hence, the relationship is linear.

Total pulmonary resistance is the sum of lung tissue resistance (R_{ti}) and airway resistance (R_{aw}):

$$R_1 = R_{\text{ti}} + R_{\text{aw}}$$

where R_1 is the pulmonary flow resistance in kPa (or cm H₂O) l⁻¹s; it is therefore the pressure difference that must be applied between the pleural surface of the lungs and the lip in order to secure a velocity of flow of 1 l⁻¹s. This quantity can be derived from the slope of the initial part of the isovolume flow–pressure curve.

Lung tissue resistance (R_{ti}) normally represents 10 % of the total pulmonary resistance. However, due to changes in airway resistance, its contribution is greater at large as compared to small lung volumes. Tissue resistance can be affected by pathology of the tissue such as in pulmonary fibrosis. It cannot be measured directly; thus, it is estimated by subtracting airway resistance from total pulmonary resistance. This estimation can be inaccurate.

Airway resistance (R_{ti}) is the sum of the resistances attributable to all airways individually. Each airway's resistance is determined by its diameter that varies with lung volume. Poiseuille's equation can provide a theoretical basis for understanding resistance of the airway. It states

$$R = \frac{8 \eta L}{\pi r^4}$$

where r is the radius of the tube, L it the length of the tube, and η is viscosity in poise.

This states that for a simple tube, the resistance is related inversely to the fourth power of the radius (Poiseuille 1840). Because in all airways the radius varies with lung size, the airway resistance varies throughout the respiratory cycle. Thus, resistance is lower at large lung volumes when the airways are expanded; it rises during expiration as the airways diminish in size and becomes infinite at residual volume when some airways close. The reciprocal of airway resistance is conductance (G_{aw}) and increases almost linearly with volume. Specific conductance (sG_{aw}) is G_{aw}/TGV where TGV is thoracic gas volume. It varies less with lung volume than G_{aw} .

In order to overcome the impedance of the respiratory system and to allow gas flow to occur, work must be performed. During breathing, the work overcomes the resistance to movement of the lungs and the chest cage. This work can be categorized by whether the energy is retained or lost from the system. The work performed to overcome the frictional resistance is dissipated as heat and subsequently lost from the system. In contrast, the work performed in overcoming elastic resistance is stored as potential energy and elastic deformation during inspiration and is usually the source of energy for expiration during both spontaneous and artificial breathing. A further discussion of resistance and gas flow will occur in the next section.

11.4 Signals for Respiratory Mechanics Measurements

11.4.1 Measurement Devices (Principles and Technical Requirements)

Our knowledge of physiology is based upon what we are able to measure. In respiratory mechanics for the most part, that is pressure and flow of gas. Modern transducer technology and the availability of computers mean that the pressure and flow can be described and modeled in detail.

This is what has led to the preeminent place of mathematical models in respiratory mechanics. However, the success of such models is only as good as the measurements upon which they are based.

The general process by which a biological signal is captured and recorded for analysis is illustrated in Fig. 11.1. A main feature of this system is the use of a transducer. A transducer is a device that transforms some signal of interest into a signal (usually electrical) that can be recorded.

11.4.1.1 Static Properties

The static properties of a transducer describe its behavior with signals that do not vary with time. In practice one deals with quasistatic signals (almost non-varying with time). However, if the signals were truly static, they would never change and it would be impossible to apply different signals to the transducer. Ideally, one would like to have a transducer that is as linear, stable, and efficient as possible, with the least amount of hysteresis and the greatest signal-to-noise ratio, resolution, and dynamic range.

The signal-to-noise ratio of a transducer is a measure that quantifies how much a signal is corrupted by noise. It is important since a transducer never produces a perfectly accurate representation of a signal. Instead, there is always a bit of unwanted contamination accompanying the measurement.

The resolution of a transducer is the smallest change it can discern in the signal it is measuring. Its dynamic range is the difference between the largest and smallest change in the input that can be accurately measured. The accuracy of a transducer is dependent on its degree of hysteresis and its stability, signal-to-noise ratio, and resolution.

The efficiency of a passive transducer relates to the ratio of the output power over the input power, while powered transducer efficiency depends upon its external power source.

11.4.1.2 Dynamic Properties

The dynamic properties of a transducer describes how its output $y(t)$ is related to its

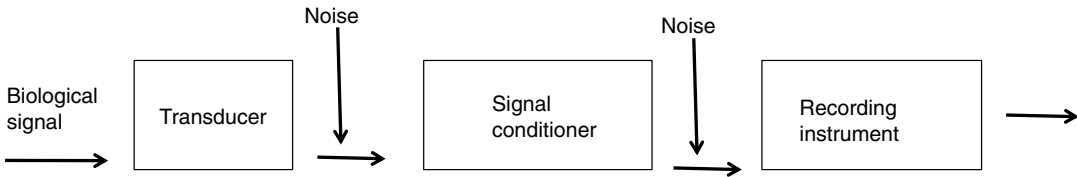


Fig. 11.1 The general process by which a biological signal is captured and recorded

input $x(t)$, when $x(t)$ varies with time (t). If the transducer is nonlinear, then its dynamic response is complex. However, with a stable linear transducer, the properties can be described in terms of its effects on input sinusoids of various frequencies.

Another important property of linear transducers is that they obey the principle of superposition, which means that the output sum of two different waveforms at the input is equal to the sum of the outputs produced by each input individually. Since any input waveform can be expressed as a sum of sinusoids (via the Fourier transform), and each of these sinusoids is altered in an amplitude and phase by an amount that depends only on frequency, the output of a linear transducer can be calculated by figuring out how each component sinusoid of the input is altered and then adding up the results.

11.4.1.3 Frequency Response

The frequency response of a transducer is a description of the way in which it alters sinusoids of different frequencies and consists of two functions $A(f)$ and $\varphi(f)$. $A(f)$ is the equivalent of the ratio A_1/A_2 above and is called the amplitude response because it is the factor by which a sinusoid of frequency f is altered in amplitude. $\varphi(f)$ is the equivalent of $\varphi_1 - \varphi_2$ above and is the corresponding alteration in its phase. Transducers can be overdamped or underdamped. The overdamped transducer has an amplitude response $A(f)$ that decreases monotonically with frequency f . When such a transducer is subjected to a sudden steplike change in the input, it responds sluggishly.

An overdamped transducer has an amplitude response $A(f)$ that increases above 1.0 on the step response before eventually falling off with increasing frequency f . When such a transducer

is subjected to a sudden steplike change in input, it responds with an overshoot and subsequent “ringing.”

11.4.1.4 Input Impedance

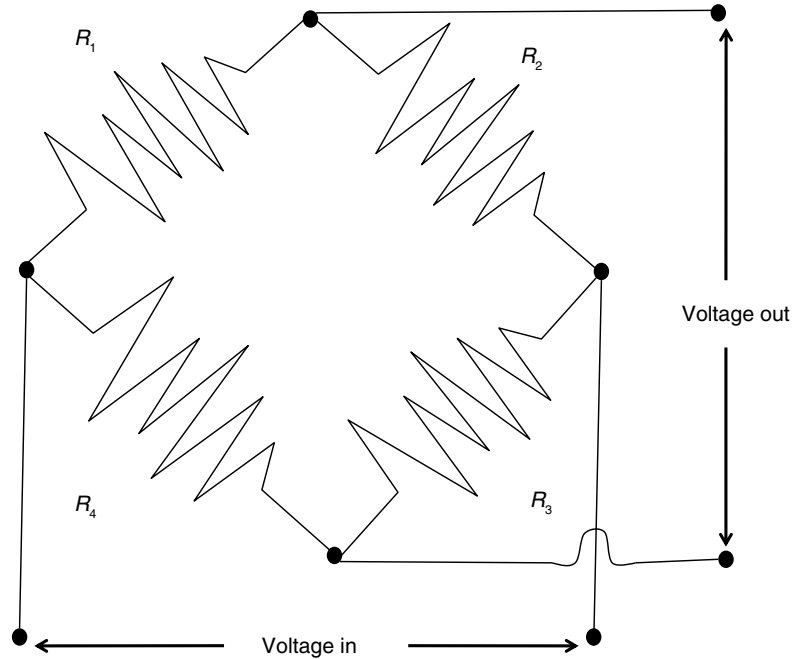
A transducer can never take the role of being a “passive observer.” Whenever a signal is measured by a transducer, the signal itself is always altered to some degree by the transducer itself because energy from the signal is required to produce a change within the transducer. The change in the input signal resulting from the presence of the transducer is inversely related to the transducers input impedance, which obviously should be as high as possible. In particular, the input impedance should be high enough that the change in the measured signal resulting from the presence of the transducer is negligible compared to the resolution of the transducer.

11.4.1.5 Analog-to-Digital Conversion

Data acquisition by a computer requires an analog-to-digital (AD) converter. This is a device that samples the incoming analog voltage signal and converts each voltage reading into a number that can be stored in the computer’s memory. AD converters have resolution depending upon its ability to convert a signal into 4,096–65,536 parts (12 bit to 16 bit converters).

The analog range of an AD converter is the voltage range over which it will accept and digitize a signal. It is desirable to have the voltage signal being sampled fill as much of the analog range of the AD converter as possible, so that the resolution of the digitized signal is maximized. If the voltage signal occupies a small fraction of the analog range, it may suffer discretization error when digitized. A digitized signal that has significant discretization error can be seen to jump about between discrete levels.

Fig. 11.2 A Wheatstone bridge circuit measuring the change in resistance of a piezoresistive strain gauge



11.4.1.6 Transducers for Measuring Pressure and Flow

Today most transducers are solid state. However, traditionally all force transducers consisted of some kind of elastic material whose deformation under the applied force is measured. A piezo-resistive force transducer (often called a strain gauge) is one whose resistivity changes as a result of an applied force. An example is a wire whose resistance increases when pulled end to end as it stretches in length and narrows in cross section. The change in resistance of a piezoresistive strain gauge is measured by making the gauge one arm of a Wheatstone bridge (Fig. 11.2). When the bridge is balanced, the output voltage is zero, which occurs when $R_1/R_2 = R_3/R_4$. As the resistance of R_1 changes, the output voltage V changes from zero. The Wheatstone bridge needs a power supply (a constant DC voltage) and the output voltage usually needs some amplification before being recorded.

The conventional device used by respiratory physiologists for measuring flow at the tracheal or airway opening is the pneumotachograph which consists of a known resistance (R) across

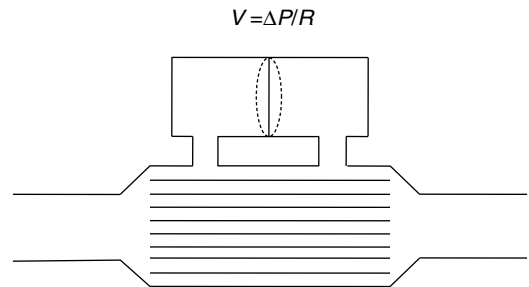


Fig. 11.3 A pneumotachograph, consisting of a differential pressure transducer to measure the drop across a known resistance. R is a known resistance across which a pressure difference is measured. Flow is then calculated by the formula in the diagram

which a pressure difference (ΔP) is measured (Fig. 11.3). The flow $\dot{V}$ through the device is then calculated as

$$\dot{V} = \Delta P / R$$

To satisfy the equation above, the known resistance inside the pneumotachograph must be designed so that the flow through it is laminar up to a certain limit. The nature of the flow

profile inside the pneumotachograph is affected by the shape of the conduit leading into it, so it is advisable to have straight lengths of tubing leading into the pneumotachograph in both directions. This conditions the flow before it reaches the point where ΔP is measured. Some pneumotachographs also contain heating elements or shells so that moisture will not condense in the resistor and change its characteristics during use.

A problem with the pneumotachograph is the frequency response of a pneumotachograph can be rather limited. If a rapidly responding pressure transducer is used with the shortest possible connection between the transducer ports and those of the pneumotachograph, the frequency response of a typical pneumotachograph may be relatively flat up to 20 Hz or so. Eventually the device achieves a resonance. It is important to keep the tubing on the pneumotachograph as short as possible.

Another aspect of the pneumotachograph that can cause problems is its input impedance. If the flow of gas required to travel between the pneumotachograph and the differential pressure transducer (in order to pressurize the latter) is significant compared to the flow through the pneumotachograph itself, then there can be significant differences between the flow through the device and the differential pressure recorded. This problem becomes worse as the diameter of the pneumotachograph decreases with the tubing and pressure transducer remaining the same. It also becomes worse as the frequency of the flow through the device increases because it may take some time for the differential pressure transducer to become pressurized via the lateral ports, resulting in phase differences between the recorded differential pressure and the flow. However, some of these limitations due to size can be overcome by utilizing a technique such as force oscillation (Schuessler and Bates 1995).

11.4.2 Airway Gas Flow

The resistance to airflow in a tube depends on the type of flow, the dimensions of the tube, and the

viscosity and density of the gas. Airflows through tubes can either be laminar or turbulent.

11.4.2.1 Laminar Flow

Laminar flow can be described as organized, and the streamlines are everywhere parallel to the sides of the tube and are capable of sliding over one another. The streamlines at the center of the tube move faster than those close to the walls, producing a flow profile that is parabolic. With laminar flow, the relation between pressure and flow is given by Poiseuille's equation:

$$P = \frac{8\eta l \dot{V}}{\pi r^4} = K_1 \dot{V}$$

or

$$\dot{V} = \left(\frac{P \pi r^4}{8 \eta l} \right)$$

where $\dot{V}$ is the flow rate; P is the driving pressure (pressure drop between the beginning and the end of the tube); r and l are the radius and the length of the tube, respectively; and η is the viscosity of the gas. Because flow resistance (R) is the driving pressure divided by the flow, the resistance with laminar flow is independent of the flow rate:

Laminar flow $P = K_1 \dot{V}$

$$R = \frac{8 \eta l}{\pi r^4} = K_1$$

Note the critical importance of the tube radius. If the radius of the tube is halved, the airway resistance increases 16-fold. Note also that laminar flow is dependent on the viscosity of gas but is independent of its density.

11.4.2.2 Turbulent Flow

Turbulent flow occurs at high flow rates and is characterized by a complete disorganization of the streamlines so that molecules of gas move laterally, collide with one another, and change velocities. Owing to this disorganization, the pressure drop across the tube is not proportionate to the flow rate as with laminar flow but rather is proportional to the square of the flow rate:

$$P = K_2 \dot{V}^2$$

Thus, the resistance to airflow is proportional to the flow rate:

$$R = K\dot{V}$$

in contrast with laminar flow. In addition, with turbulent flow, there is an increase in the pressure drop for a given flow, but the viscosity of the gas becomes unimportant.

11.4.2.3 Reynolds Number

Whether the airflow is laminar or turbulent depends to a large extent on a dimensionless quantity called the Reynolds number, Re , which is given by

$$Re = \frac{2 r v d l}{\eta}$$

where r is the radius of the tube, v is the average velocity, d is the density of the gas, and η is the viscosity of the gas. In a straight, smooth, rigid tube, turbulence occurs when Re exceeds 2,000.

In the lung, laminar flow occurs only in small peripheral airways, where, owing to the

large overall cross-sectional area, flow through any given airway is extremely slow. Turbulent flow occurs in the trachea. In the remainder of the lung, owing in large part to the multiple branching of the tracheobronchial tree, flow is neither laminar nor turbulent but rather mixed or transitional. With transitional flow pattern, flow is dependent on both the viscosity and the density of the gas:

$$P = K_1 \dot{V} + K_2 \dot{V}^2$$

11.4.2.3.1 Threshold Resistors

A threshold resistor is a resistor that allows no gas to pass until a threshold pressure is reached. Once that pressure is reached, gas passes freely with little further rise in pressure as the flow rate increases. The Starling valve (Fig. 11.4) is the classic prototype of the threshold resistor. In this model gas will only flow when the upstream pressure exceeds the pressure in the chamber surrounding the collapsing tubing. Another example of a threshold resistor is a spring-loaded valve that was commonly used in ventilators to maintain end-expiratory pressure.

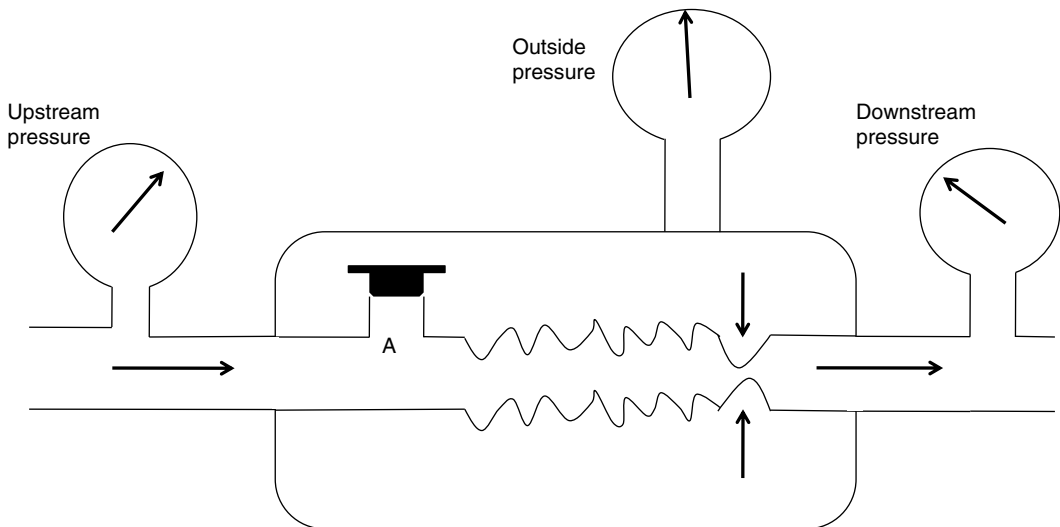


Fig. 11.4 The Starling resistor consists of a length of a flaccid collapsible tubing passing through a rigid box. When the outside pressure surrounding the tube exceeds the upstream pressure, the tubing collapses as illustrated by the arrows. Thus, no gas can flow no matter the level of

downstream pressure. If orifice A is opened, the outside pressure rises with the upstream pressure and so limits flow rate to a level which is independent of the magnitude of the upstream pressure

Another property of the threshold resistor is that once gas begins to flow, an increase in downstream pressure will distend the tubing thus decreasing the resistance of the device. However, a decreased downstream pressure cannot initiate flow. This model can also be used to explain the behavior of a collapsing airway during expiration.

11.4.3 Airway Pressure

The airway pressure is the force that the mechanical ventilator and patient apply on the respiratory system. The measurement requires of a pressure transducer. Pressure transducers used in clinical practice are essentially of two types: (1) variable reluctance transducer, where an element is deformed by the pressure changing the magnetic flux linkage between two coils receiving electrical current, and (2) piezoresistive transducers where there is an element that when deformed changes the resistance to electrical current.

The airway pressure (P_{aw}) may be measured at different points of the mechanical ventilator-patient circuit. A pressure sensor or transducer may be placed at the airway opening, P_{AO} (the Y-piece just before connecting to the endotracheal tube); at the inspiratory or expiratory ventilator outlets; or at the trachea (using a catheter). The place of measurement of airway pressure may yield different results, as the effects of the interface (circuit, humidifier, and endotracheal tube) may interfere with the measurements. Almost all current mechanical ventilators have sensors for airway pressure; if absent, P_{aw} can be measured with stand-alone devices.

The effect of flow in the accuracy of airway pressure measurements must be accounted. During dynamic conditions, there is flow as a result of a driving pressure. The effect of flow and the position of the pressure transducer are described by the Bernoulli effect. If a catheter or an opening in the system, where the pressure is going to be measured, is perpendicular to the direction of flow, the value measured is the lateral pressure (P_{lat}) rather than the driving pressure. The following equation demonstrates the factors that affect the P_{lat} . The P_{lat} is lower than

the driving pressure, unless there is no flow (P_{stat}), or if the cross-sectional area where the pressure being measured is large.

$$P_{lat} = P_{stat} - \frac{\beta \rho \dot{V}^2}{2A^2}$$

where P_{stat} is the static pressure, A is cross-sectional area, $\dot{V}^2$ is flow, ρ is density of the gas, and β is the flow velocity profile (1 = linear, 2 = parabolic).

The Bernoulli effect can be eliminated by the use of an opening or catheter for measurement that faces the flow; this is called a pitot tube. By facing the flow, the opening of the tube makes a small amount of gas to stop, and hence, the effect of flow is eliminated and we can measure P_{stat} .

The P_{aw} is the transrespiratory system pressure and is a manifestation of the respiratory system characteristics (elastic P_{EL} and resistive P_R):

$$P_{aw} = P_{EL} + P_R$$

This can be written as

$$P_{aw} = \left(\frac{V}{C} + P_{EX} \right) + \dot{V}R$$

where V indicates volume relative to the end-expiratory position, C is compliance, P_{EX} is end-expiratory alveolar pressure, $\dot{V}$ is flow, and R is resistance.

During static conditions, the airway pressure is a manifestation of the respiratory system compliance:

$$P_{aw} = P_{EL},$$

or

$$P_{aw} = \left(\frac{V}{C} + P_{EX} \right) = P_{plat}$$

During mechanical ventilation, the airway pressure signal (Fig. 11.5) may be used to obtain direct measurements (peak inspiratory pressure, plateau pressure) or calculated parameters (mean airway pressure).

The peak inspiratory pressure (PIP) is the maximum pressure during assisted ventilation. According to the mode of ventilation, the value may represent different respiratory system characteristics. In a volume- or flow-controlled mode,

Fig. 11.5 Airway pressure signal according to mode of ventilation

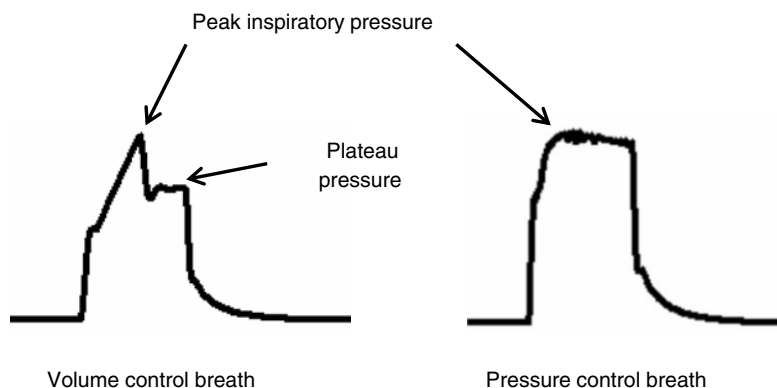
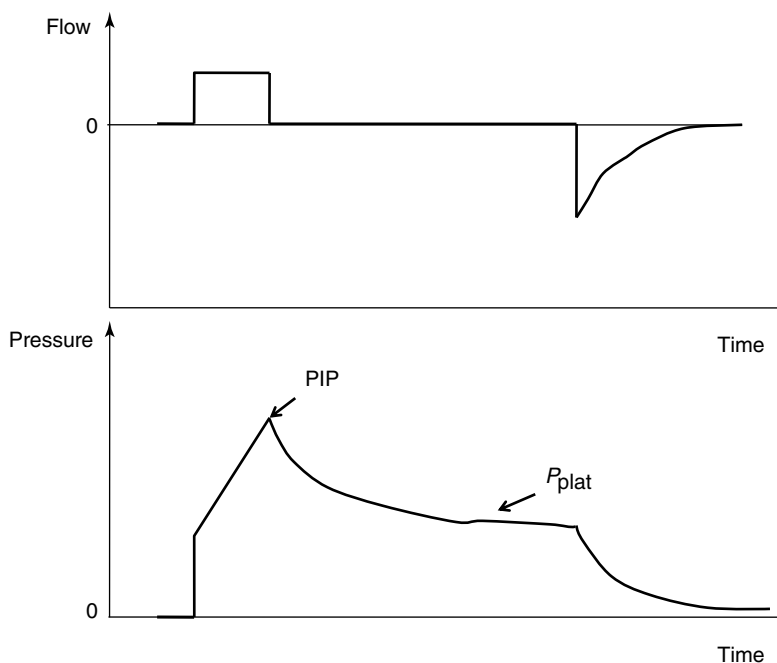


Fig. 11.6 The figure shows flow–time and pressure–time waveforms from a constant flow mode of ventilation and illustrates various landmarks for the waveform



the PIP is the manifestation of the respiratory system compliance, resistance, and patient effort (Fig. 11.6). In a pressure-controlled mode, the PIP is a manifestation of the operator set inspiratory pressure.

The plateau pressure, P_{plat} , is the airway pressure during an inspiratory hold while a patient is on mechanical ventilation. By creating an inspiratory hold, the effects of lung resistance and impedance are annulled, leaving a measure of the respiratory system compliance. As described before, the respiratory system compliance is a manifestation of the lung, chest wall, and abdomen.

The mean airway pressure, $\bar{P}_{aw}$, is the average pressure of the airway over a given time interval. In a static model, where all the breaths are identical, the mean airway pressure is the area under the curve of a pressure–time curve for one breath divided by the total cycle time (inspiration + expiration). In an active model, the mean airway pressure can be calculated as an average over several breaths. Several mechanical ventilators will display a $\bar{P}_{aw}$ value; it depends on the brand of mechanical ventilator and the technique it uses to measure it. Some use a number of breaths, while others do it breath to breath. To obtain the measurement, the

ventilator or measuring instrument must average a large number of pressure measurements.

The formula to calculate P_{aw} is

$$\bar{P}_{aw} = \left(\frac{1}{TT} \right) \int_{t=0}^{t=TT} \bar{P}_{aw} dt$$

where TT is the total cycle time in seconds.

The $\bar{P}_{aw}$ will be affected by the PIP, PEEP, type of pressure waveform, frequency, and inspiratory and expiratory time. The larger the PIP, PEEP, frequency, and inspiratory time, the higher the $\bar{P}_{aw}$. The larger the PEEP, the lower the $\bar{P}_{aw}$. The closer the waveform is to a perfect square, the higher the $\bar{P}_{aw}$. At a single-compartment level with linear equal inspiratory and expiratory resistance, $\bar{P}_{aw}$ is equal to the mean alveolar pressure. If the inspiratory resistance is higher than the expiratory resistance, the $\bar{P}_{aw}$ will be higher than the mean alveolar pressure. If the expiratory resistance is higher than the inspiratory resistance, the $\bar{P}_{aw}$ will be lower than the alveolar pressure.

11.4.4 Transesophageal Pressure (Meaning and Measurement)

The esophagus lays in the posterior mediastinum inside the thorax and is surrounded by a scant amount of soft tissue and the pleura. Its location allows to use transducers to obtain pressure measurements (Fig. 11.7). The changes in esophageal pressure, ΔP_{es} , correlates and is used as a surrogate for the changes in intrapleural pressure, ΔP_{pl} . The position of the patient (supine versus prone or standing), type of catheter used, and underlying condition may affect pleural pressures (Washko et al. 2006). Nonetheless, P_{es} as a surrogate of P_{pl} allows the practitioner to obtain and calculate and separate the lung and chest wall compliances from the respiratory system compliance. As follows,

$$C_{RS} = \frac{\Delta V}{\Delta(P_{AO} - P_{BS})}$$

where ΔV is change in volume, P_{AO} is the pressure at the airway opening, and P_{BS} is pressure at the body surface. During mechanical ventilation, this value is $\Delta V = V_t$, and $\Delta(P_{aw} - P_{BS})$ is

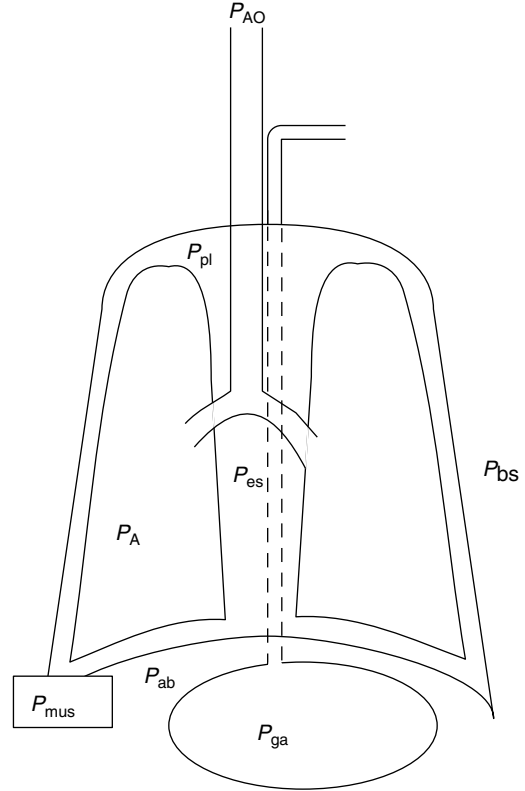


Fig. 11.7 Diagram of the respiratory system: P_{AO} pressure at the airway opening, P_{pl} pleural pressure, P_{es} esophageal pressure, P_{bs} body surface pressure, P_A alveolar pressure, P_{mus} muscle pressure, P_{ab} abdominal pressure, P_{ga} gastric pressure

($P_{plat} - PEEP_{TOT}$) (in the setting of mechanical ventilation, P_{BS} can be substituted by total PEEP). If we take into consideration the P_{es} as a marker of P_{pl} , then we can divide the respiratory system compliance into lung and chest wall:

$$C_L = \frac{\Delta V}{\Delta(P_{AO} - P_{es})}$$

$$C_{CW} = \frac{\Delta V}{\Delta(P_{es} - P_{BS})}$$

The measurement of the esophageal pressure can be done with a balloon-tipped catheter, a liquid-filled catheter, or a transducer at the tip of a catheter. The most common method is the balloon-tipped catheter.

The placement of an esophageal balloon is essential to obtain consistent measurements. The

catheter is inserted under topical lubrication and in some cases topical anesthesia through the nose. The catheter is advanced to the gastric chamber, where, if the patient is actively breathing, the balloon will demonstrate positive deflections (the abdominal pressure increases during inspiration). The esophageal catheter is then retrieved until negative deflections are seen; from that point one must retract the esophageal balloon the amount of distance to maintain the whole balloon in the thoracic esophagus. It is essential to use low volumes to inflate the balloon (<1 cc air) as this will cause false elevation in the measurements.

To ensure that the balloon catheter is appropriately placed, the patient or clinician must generate transpulmonary pressure swings so that the ΔP_{es} and ΔP_{AO} can be compared. In a patient who can cooperate, the maneuver consists of measuring the P_{AO} and P_{ES} simultaneously while the patient performs forceful breathing efforts. The most common test used to assess accuracy is the dynamic "occlusion test." It is performed by occluding (blocking) the airway while 3–5 respiratory efforts happen. The ΔP_{es} and ΔP_{AO} are then compared. A ratio of difference between $\Delta P_{es}/\Delta P_{AO}$ should approach 1 to ensure measurement agreement.

11.4.4.1 Alveolar Pressure

Direct measurement of alveolar pressure in patients is not feasible but has been performed in animal studies. Subpleural alveolar pressure (P_A) is measured using an alveolar capsule technique. A small plastic capsule is attached to the exposed pleural surface and a small area is punctured with a needle and isolated so changes can be measured utilizing a small piezoresistive pressure transducer. Multiple sites can be measured simultaneously.

11.5 Measurement of Passive Respiratory Mechanics

11.5.1 Mechanics of the Passive Respiratory System

The two most common methods of measuring passive mechanics are the single and multiple occlusion techniques. For the occlusion technique, the

Hering–Breuer reflex must be invoked to elicit relaxation of the respiratory system, thus allowing accurate assessment of respiratory mechanics measurements. To perform these techniques, airflow, pressure, and volume changes at the mouth must be recorded and analyzed.

As stated previously a model of the respiratory system is considered passive because the lungs respond to forces external to the lungs. The single-compartment linear model is linear because its independent variables (V and $\dot{V}$) are linearly related to the dependent variable P .

$$P = EV + R\dot{V} + P_0$$

The single-compartment linear model can be made more realistic by adding extra features in two ways: (1) by making it nonlinear and (2) by adding more mechanical degrees of freedom.

The resistive pressure drop can be made nonlinear as follows, which includes two resistive parameters and flow squared:

$$\Delta P = K_1\dot{V} + K_2\dot{V}^2$$

This equation is used to describe a conduit with both laminar and turbulent fluid flow known as the Rohrer's equation.

Further, the elastic pressure nonlinear can be converted as follows:

$$E = L_1V + L_2V^2$$

11.5.2 Resistance, Compliance, Inertance, Tissue Damping, and Elastance

11.5.2.1 Resistance

Resistance during mechanical ventilation describes the airflow conditions during both inspiration and expiration. Resistance represents the flow-resistive elements of the respiratory system. It is expressed as a pressure variation over gas flow using the following general equation:

$$\text{Resistance} = \frac{\Delta \text{Pressure}}{\text{Flow}}$$

By substituting standard units, it becomes

$$\text{Resistance} = \frac{\text{cm H}_2\text{O}}{\text{ml} \cdot \text{s}^{-1}}$$

Flow, tidal volume, and the dimensions of the ventilator and airway components affect airway resistance. The size of the endotracheal tube is an important element in gas flow through the breathing circuit and thus affects the measured resistance. When delivering a set tidal volume, the volume at a set flow is affected by a smaller and longer tube that will produce larger resistance to gas flow.

11.5.2.1.1 Compliance and Elastance

Compliance is how much a compartment will expand if the pressure in that compartment is changed. A balloon has a high compliance because a small pressure increase inside the balloon will greatly expand the balloon. A rigid tube has a low compliance because a small pressure increase inside the rigid tube will not result in a significant increase in the volume of the rigid tube. Two major forces contribute to lung compliance: tissue elastic forces and surface tension forces. The compliance (C) is determined by the change in elastic recoil pressure (ΔP) produced by a change in volume (ΔV):

$$C = \frac{\Delta V}{\Delta P}$$

The compliance of the lungs (C_L), chest wall (C_{CW}), and respiratory system (C_{RS}) can be determined by measuring the change in distending pressure and the associated change in volume. The distending pressure represents the pressure change across the structure. Where P_{ao} , P_{pl} , and P_{bs} represent the pressure measured at the airway opening, pleural pressure, and pressure at the body surface (atmospheric pressure), respectively.

$$C_L = \frac{\Delta V}{\Delta(P_{ao} - P_{pl})}$$

$$C_{CW} = \frac{\Delta V}{\Delta(P_{pl} - P_{bs})}$$

$$C_{RS} = \frac{\Delta V}{\Delta(P_{ao} - P_{bs})}$$

Lung volume and volume–pressure relationships (e.g., compliance) reflect parenchymal (air space) development, whereas airflow and pressure–flow relationships (resistance and conductance) predominantly reflect airway development. The lungs become stiffer (compliance decreases) at higher lung volumes.

Total respiratory compliance (C_{rs}) is related to lung compliance and chest wall compliance by the following equation:

$$\frac{1}{C_{rs}} = \frac{1}{C_{pulm}} + \frac{1}{C_{CW}}$$

Total static compliance (during no flow activity at the end of inspiration and expiration) and total dynamic characteristics (during active inspiration) are usually monitored via a volume–pressure relationship during mechanical ventilation.

11.5.2.2 Chest Wall Compliance

Chest wall compliance (C_{CW}) describes the changes in tidal volume (V_T) relative to the pleural pressure, reflected by the esophageal pressure (P_{eso}), and is expressed by the following equation:

$$C_{CW} = \frac{V_T}{P_{eso}}$$

To calculate chest wall compliance, the patient should be completely passive. In patients this is usually accomplished by the use of a neuromuscular blocking agent or inducing apnea by hyperventilation, thus removing respiratory drive. Chest wall compliance is an essential component in the calculation of total work of breathing.

11.5.2.3 Lung Compliance

Lung compliance (C_{pulm}) describes the changes in tidal volume relative to transpulmonary pressure $P_{plat} - P_{eso}$ where P_{plat} is the plateau pressure, also referred to as the alveolar pressure, and P_{eso}

is the esophageal pressure under quasistatic conditions.

Lung compliance is expressed by the following equation:

$$C_{\text{pulm}} = \frac{V_T}{P_{\text{plat}} - P_{\text{eso}}}$$

Lung compliance can be obtained on passively or spontaneously breathing patients.

11.5.2.4 Elastance

Elastance is defined as the change in distending pressure divided by the associated change in volume:

$$E = \frac{\Delta P}{\Delta V}$$

Elastance is therefore the reciprocal of compliance; thus, stiff lungs have a high elastance. The end-inspiratory airway occlusion method is clinically used to measure the static compliance of the respiratory system or its reciprocal, elastance of the respiratory system ($E_{\text{st,rs}}$), according to the following equation (Rossi et al. 1998):

$$E_{\text{st,rs}} = \frac{(P_{\text{plat}} - \text{PEEP}_i)}{V_T}$$

where P_{plat} is plateau pressure obtained after occlusion of the airway, PEEP_i is intrinsic positive end-expiratory pressure (PEEP), and V_T is tidal volume.

11.5.2.5 Inertance

Inertance of the respiratory system is the analog of inertia and is a measure of the tendency of the respiratory system to resist changes in flow. Forces due to inertance increase with increasing frequency, and since they are opposite in direction to those forces produced by elastance, resistance is thus reduced. At normal respiratory frequencies, inertance is usually insignificant. The inertance I therefore equals $L \times \rho / A$. The pressure drop due to inertance is greatest when the flow increases rapidly, as occurs if the frequency of breathing rises.

11.5.2.6 Tissue Damping

Tissue damping is closely related to tissue resistance and reflects the energy dissipation in the lung tissues. Tissue damping is independent of frequency. In a constant phase model, the calculation of input impedance is

$$z(f) = R_{\text{aw}} + i2\pi f I_{\text{aw}} + \frac{G_t - iH_t}{(2\pi f)^\alpha}$$

where

$$\alpha = \left(\frac{2}{\pi} \right) \arctan \left(\frac{H_t}{G_t} \right)$$

R_{aw} represents the resistance of the pulmonary airways to gas flow, I_{aw} is the inertance of the gas in the airways, G_t (tissue damping) characterizes viscous dissipation of energy within the lung tissues during inflation and deflation, and H_t (tissue elastance) characterizes energy storage in the tissues. G_t is thus related to tissue resistance, while H_t is related to tissue elastance.

11.5.3 Dynamic Hyperinflation

When breathing on the ventilator with increased time constants secondary to increased inspiratory resistance, hyperinflation develops secondary to incomplete emptying of the lung during expiration. For the patient to generate inspiratory airflow in the next breath, the patient must generate a negative pressure equal in magnitude to the opposing elastic recoil pressures. Secondary to these increased elastic load related to the patient, there is a shift in their compliance curve to the upper less compliant part of the curve. This coupled with a decrease in the efficiency of force generation by their respiratory muscles increases their work of breathing. In a patient breathing on the ventilator, this elevated static recoil pressure leads to intrinsic PEEP or static PEEP_i . PEEP_i poses a significant inspiratory threshold that has to be fully counterbalanced by increasing inspiratory muscle effort in order to generate a negative pressure in the central airways in order to trigger the ventilator.

11.5.4 Principals and Practice of Classical Measurement of Respiratory System

Most techniques for measuring the mechanics of the respiratory system are based on the assumption that a single balloon on a pipe can model the lung. When breathing is simulated in this model, the balloon is inflated and deflated and the dynamics of the system may be described by the general equation of motion for a linear single-compartment model (SCM):

$$P = EV + R\dot{V} + I\ddot{V}$$

That is, the driving pressure of the system (P) is the sum of its elastic ($EV = \text{elastance} \times \text{volume}$), resistance ($R\dot{V} = \text{resistance} \times \text{flow}$), and inertive ($I\ddot{V} = \text{inertance} \times \text{acceleration}$) components. For the most practical applications, the contribution of inertance in this equation is negligible and can be ignored. Thus, the equation can be written as follows:

$$P = EV + R\dot{V}$$

If we apply this equation to the respiratory system during mechanical ventilation, dynamic elastance (E_{RS}) (or compliance (C_{RS})) and dynamic resistance (R_{RS}) may be estimated by relating pressure measured at the airway opening (P_{ao}) to simultaneous measurements of flow ($\dot{V}$) and volume (V).

The equation of motion for an SCM of the respiratory system is as follows:

$$P_{ao} = E_{RS}V + R_{RS}\dot{V} \quad (11.11)$$

or

$$P_{ao} = \frac{1}{C_{RS}}V + R_{RS}\dot{V}$$

Similarly, dynamic lung elastance (E_l) and lung resistance (R_l) may be calculated by relating transpulmonary pressure (P_{tp}) to flow and volume. The P_{tp} may be calculated by subtracting pleural pressure estimate from and esophageal catheter (P_{es}) from airway opening pressure

measurements ($P_{tp} = P_{ao} - P_{es}$). The equation of motion for an SCM of the lung is

$$P_{tp} = E_lV + R_l\dot{V}$$

11.5.5 Simplified Methods to the Measurement of Total Respiratory Mechanics

There are a number of published articles describing different techniques to measure dynamic respiratory mechanics in children. Below is a summary of some of those techniques.

11.5.5.1 Mead–Whittenberger Technique

Traditionally this technique has been used to measure dynamic compliance (C_{dyn}) and resistance (R_{dyn}) in spontaneously breathing subjects (Mead and Whittenberger 1953). This technique assumes that resistance and compliance are constant throughout inspiration and expiration. Changes in transpulmonary pressure (P_{tp}) are related to changes in flow and volume over the tidal volume range. Compliance is calculated by examining the points of zero flow at end-inspiration and end-expiration. The pressure change and corresponding volume change between these points can be used to determine dynamic compliance, $C_{dyn} = \Delta V / \Delta \dot{V}$, and is measured during expiration. Similarly, dynamic resistance is measured as a change in flow between points of equal volume in the mid-volume range $R_{dyn} = \Delta P / \Delta \dot{V}$. Under these conditions elastic forces are assumed to be equal and opposite.

A limitation of this technique is that the assumption of equality of resistance and compliance throughout both inspiration and expiration may not be true for measurements with evidence of hyperinflation. This may be difficult to apply to ventilated subjects as the points when flow = 0 at mid-tidal and end-tidal volume occur with rapidly changing pressure patterns. Some of these limitations may be overcome utilizing the technique of handbagging the patient during the measurement.

11.5.5.2 Mortola–Saetta Method

This is a method which is a variation of the least-squares regression technique described below. This technique involves occluding the airways of spontaneously breathing subject at end-expiration with a resultant inspiratory effort against the occlusion. This effort results in a pressure change, which is thought to reflect the driving pressure of the respiratory system. When pressure is measured at known intervals from the beginning of inspiration, it can be by the measurement of volume from the corresponding time points during the previous unoccluded breaths and plotted against the flow/volume relationship. In this model, the slope of this relationship is a measure of lung resistance and the intercept is a measure of lung elastance (Mortola and Saetta 1987).

11.5.5.3 Volume Corrected Resistance

As can be inferred by the name, this technique corrects the measurement of resistance from the pressure–flow relationship for changes over the tidal volume range. By plotting pressure divided by flow (R_{dyn}) against volume, resistance can be examined over the tidal volume range (Beardsmore et al. 1986).

11.5.5.4 Forced Oscillation Technique

Forced oscillation technique is a general term for methods that apply broadband flow signals to the airway opening, with a measure of the resulting pressure also at the airway opening or at the body surface (Solyman et al. 1989). This technique allows the calculation of respiratory impedance that includes both the resistive and elastic properties of the system. This technique requires a signal-producing device that is usually either done with a loud speaker or a piston oscillator.

The key measurement considerations when implementing the forced oscillation techniques relate to characteristics of the flow transducer, filtering, error reduction, and sampling. For this technique pressure and flow transducers must be linear over the range of interest. The frequency response of pressure and flow transducers must be adequate over the frequency range investigated. Most importantly, they must be matched. The

dynamic common mode rejection ratio of the flow transducer must be high over the frequency range of interest (i.e., input impedance must be high). Appropriate filtering for anti-aliasing must be done, so as to satisfy the sampling theorem. In order to minimize discretization error, the pressure and flow signals must be suitably amplified to occupy a significant fraction of the A/D converter range. Data must be sampled at greater than twice the highest frequency of interest.

The best implementation of the forced oscillation technique requires careful construction of the perturbation signal. This is the flow to be applied to the lungs, and the preferred approach for its constructing is to use composite signals consisting of sums of sine waves; thus,

$$\dot{V}(t) = \sum_{i=1}^n A_i \sin(2\pi f_i t + \phi_i)$$

The frequencies (f_i) of the sine waves are distributed across frequency range of interest. The amplitudes (A_i) of the sine waves are chosen to give good signal to noise at each frequency of interest (e.g., constant). The phases (ϕ_i) of the sine waves may be chosen randomly. For example, the sine waves can be selected to try to minimize the peak–peak excursions in the final flow signal.

11.5.5.5 Passive Flow–Volume Technique

The passive flow–volume technique involves invoking the Hering–Breuer inflation reflex to relax the respiratory muscles at the end-inspiration after occlusion of the airway (LeSouef et al. 1984). Pressure is measured during this occlusion and the resultant flow–volume relationship during passive expiration is examined. The slope of the flow–volume relationship during passive expiration is examined. The slope of the flow–volume profile during expiration is the expiratory time constant (τ_{exp}), and the extrapolation of this slope to zero flow allows the estimation of the FRC. Compliance is calculated from the ratio of the volume above FRC, at which the occlusion was made, to the end-inspiratory recoil pressure at this volume. Resistance is then calculated by relating (τ_{exp}) to the measured compliance ($\tau_{\text{exp}} = RC$; $R = \tau_{\text{exp}}/C$). This assumes

a linear relationship over the volume range measured and the inactivity of respiratory muscles during expiration. This assumption is obviously fulfilled when performed in paralyzed subjects; however, the resistive properties of the endotracheal tube may affect the shape of the flow–volume curve especially when a small endotracheal tube is used in infants (Brown et al. 1989).

11.5.5.6 Interrupter Technique

In order to partition respiratory resistance into components representing the conducting airways (R_{aw}) and a peripheral phenomena representing the tissue viscoelastic components P_{dif} , an interrupter technique with occlusion of the airway during expiration can be utilized (Sly and Bates 1988). When the airway is occluded during expiration, there is an initial rapid jump in pressure after occlusion (P_{int}). A slower, secondary rise in pressure to a plateau occurs after occlusion (P_{dif}). This component represents stress recovery within the tissues and the chest wall as well as any redistribution of gas (pendelluft) occurring between different lung units. Thus, this technique allows measurement of R_{aw} (airway resistance including endotracheal tube and chest wall resistance), static elastance, and the viscoelastic properties of the lung from each occlusion. It is important to note that respiratory muscle activity may affect the accuracy of these measurements.

11.5.6 Respiratory Mechanics by Least-Squares Fitting

The single-compartment model of the respiratory system captures the essential mechanical feature of the respiratory system; it can be inflated and deflated to mimic breathing. This model has a single mechanical freedom because its state is completely defined by its compartmental volume. Figure 11.8 illustrates a single-compartment linear model. In this model by choosing the dimensions of the conduit appropriately, we can give it a resistance similar to any particular set of pulmonary airways. By choosing the stiffness of the spring appropriately, we can give the compartment an elastance similar to that of a real lung.

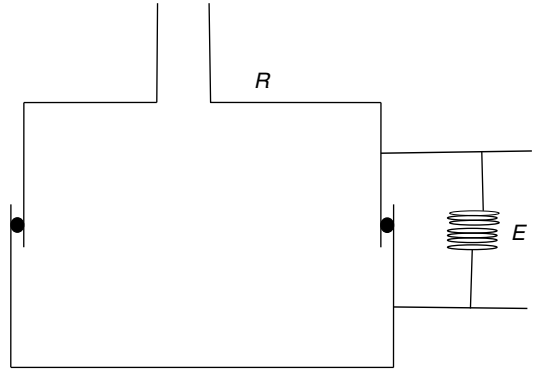


Fig. 11.8 Single-compartment linear model. R is the resistance of conduit and E is elastance illustrated as a spring. The stiffness of the spring offers an elastance similar to the lung. In this model R is resistance and is controlled by choosing the dimensions of the conduit. E is elastance and is determined by the stiffness of the spring

Utilizing fitting models to data by least squares, we can make the single-compartment linear model behave like a real respiratory system. If the model were to be driven by the same flow signal as the real system, it would require a pressure signal that is similar to that applied to the real system. This is achieved by choosing appropriate values for the model parameters resistance (R), elastic (E), resting pressure (P_0). The values chosen are required that the behavior of the model matches that of the real system in the “least-squares sense.” Fortunately, for the single-compartment linear model, this can be done by multiple linear regressions.

The least-squares regression method of measuring resistance involves relating the driving pressure of the system (P_{dr}) to the corresponding flow (Mortola et al. 1982). Driving pressure is corrected by subtracting the contribution of the elastic and viscoelastic pressure components from transpulmonary pressure (P_{tp}). Then P_{dr} is plotted against flow, and linear regression is used to determine the slope that is the resistance of the system. This technique also assumes a linear relationship of the data. Most physical systems will exhibit approximately linear behavior provided they operate within a sufficiently modest amplitude range. When a system is forced to operate over a large amplitude range, its behavior often becomes highly nonlinear.

Least mean squares analysis minimizes the mean squared error between the measured pressure and the calculated pressure for each sampled point using a particular equation. Multiple linear regressions allow multiple independent variables to be simultaneously included in the regression calculation.

11.5.7 Practical Application and Result Interpretation

Measurement of respiratory mechanics in a relaxed ventilated patient can be obtained using the technique of rapid airway occlusion during constant flow inflation (Rossi et al. 1985a). Rapid airway occlusion at the end of a passive inflation produces an immediate drop in both airway pressure (P_{aw}) and transpulmonary pressure (P_l) from a peak value (P_{peak}) to a lower initial value (P_{init}) followed by a gradual decrease until a plateau (P_{plat}) is achieved after 3–5 s (Rossi et al. 1985b) (Fig. 11.9). P_{init} is measured by back extrapolation of the slope of the latter part of the pressure tracing to the time of the airway occlusion. P_{plat} on the P_{aw} , P_l , and pleural pressure (P_{es}) tracings represent the static end-inspiratory recoil pressure of the total respiratory system, lung, and chest wall, respectively.

11.5.7.1 Elastance/Static Compliance

Total static compliance of the respiratory system ($C_{st,tot}$) is frequently measured and monitored during mechanical ventilation. Total static compliance is the pressure to overcome the elastic forces of the respiratory system for a given tidal volume and under a zero flow (static) condition. The end-inspiratory airway occlusion method is clinically used to measure static compliance of the respiratory system or its reciprocal, elastance of the respirator system ($E_{st,rs}$), according to the following equation (Foti et al. 1997):

$$E_{st,rs} = \frac{(P_{plat} - PEEP_i)}{V_T}$$

where P_{plat} is plateau pressure obtained after occluding the airway. $PEEP_i$ is intrinsic PEEP and

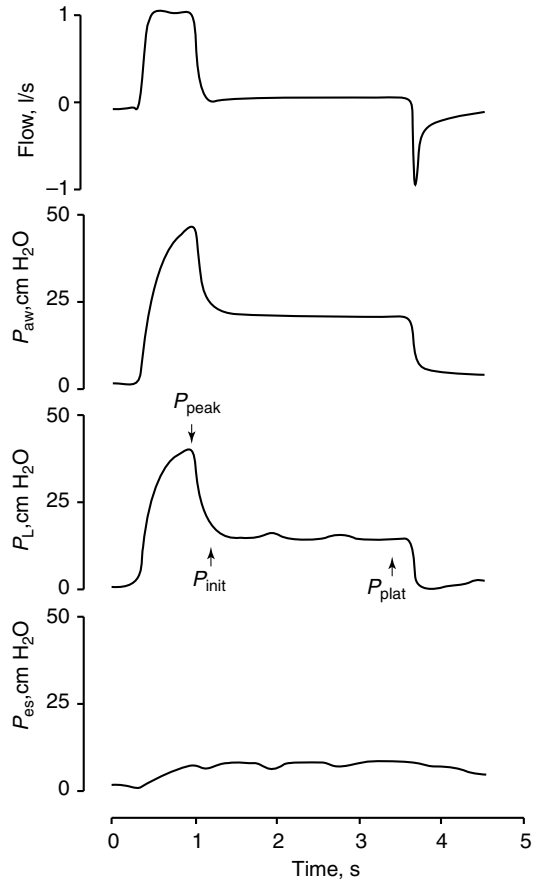


Fig. 11.9 Flow (inspiration upward), P_{aw} , P_l , and P_{es} tracings in a representative patient during passive ventilation. An end-inspiratory occlusion produced a rapid decline in both P_{aw} and P_l from P_{peak} to a lower P_{init} , followed by gradual decrease to P_{plat} (From Jubran and Tobin (1997))

V_T is tidal volume. Using an esophageal balloon catheter, $E_{st,rs}$ can be partitioned into its lung and chest wall components by dividing $(P_{plat} - PEEP_i)$ by V_T on the P_l and P_{es} tracings, respectively.

Specific measuring conditions must be met for a valid static compliance value including passive tidal volume (inspiration and expiration) and compressible volume correction for tubing; the plateau must have an end-inspiratory pause of at least 1 s with a stable pressure within 0.5 cm H₂O over 2 readings at least 10 ms apart.

Changes in static compliance are associated with changes in lung elasticity; lung pathology that increases lung recoil or decreases lung volume will decrease the static compliance.

11.5.7.2 Dynamic Compliance

Formerly known as the effective dynamic compliance, the dynamic characteristics (DynChar) can be derived by dividing the ventilator delivered V_T by (peak P_{aw} – PEEP). Since the relationship of volume versus pressure during a dynamic event is subject to resistive forces inside the system, it is not considered a measure of dynamic compliance.

Total dynamic characteristics describe the components of total lung or parenchymal compliance plus the pressure required to overcome the airway resistance in the delivery of a tidal volume. Dynamic characteristics thus reflect resistive and elastic properties of the respiratory system. It is the tidal volume relative to the peak airway pressure under a dynamic condition and is expressed by the following relation:

$$\text{DynChar} = \frac{V_T}{\text{PIP} - \text{PEEP}}$$

Trended values are thus clinically helpful reflecting resistive and elastic properties of the respiratory system.

Figure 11.10 is a volume–pressure loop from a constant flow mode of ventilation. The slope of AC reflects the total dynamic characteristics of the respiratory system.

The difference between static compliance and dynamic characteristics can be used as an indirect index of flow-resistive properties of the respiratory system.

Alternatively, dynamic elastance of the respiratory system ($E_{\text{dyn,rs}}$) can be obtained by dividing the difference in P_{aw} at points of zero flow by delivered V_T (Nicolai et al. 1993). Accordingly, $E_{\text{dyn,rs}}$ can be computed according to the formula:

$$E_{\text{dyn,rs}} = \frac{P_{\text{init}} - \text{PEEP}_i}{V_T}$$

$E_{\text{dyn,rs}}$ can be partitioned into its lung ($E_{\text{dyn,L}}$) and chest wall components by dividing ($P_{\text{init}} - \text{PEEP}_i$) pm P_i and P_{es} tracings.

11.5.7.3 Pressure–Volume Curves

A pressure–volume curve of the respiratory system can be constructed in a paralyzed patient by

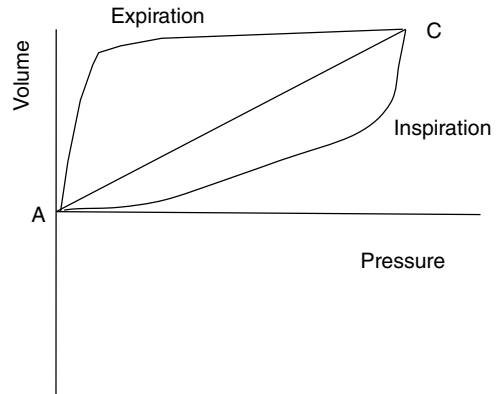


Fig. 11.10 Volume–pressure loop from a constant flow mode of ventilation. The slope of AC reflects the total dynamic characteristics of the respiratory system. Pressure–volume loop of patient’s lung with acute respiratory distress syndrome

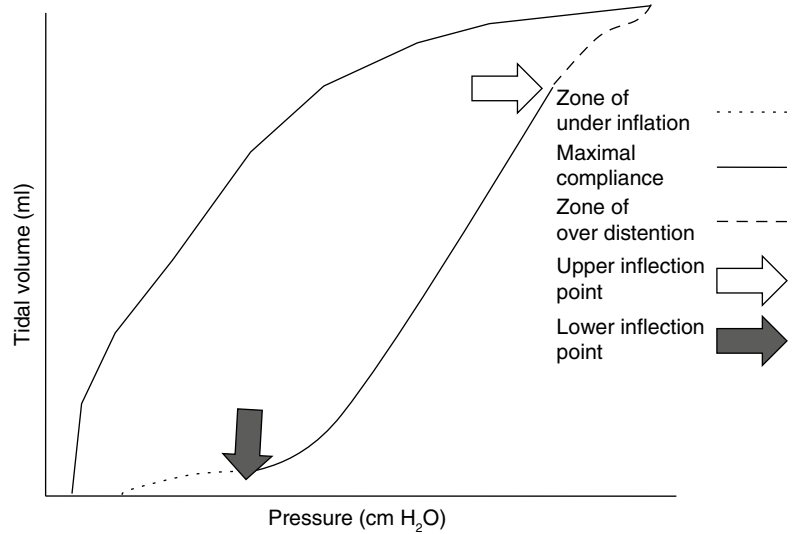
measuring the airway pressure as the lungs are progressively inflated with a 1.5–2 l syringe. A lower inflection point and an upper inflection point may be seen on the pressure–volume curve (Fig. 11.11) (Mergoni et al. 2001). A lower inflection point is thought to reflect the point at which small airways and alveoli reopen, corresponding to closing volume. It has been recommended that the PEEP level should be set slightly above this closing volume (Mergoni et al. 2001).

11.5.7.4 Resistance

Airway resistance can be measured in ventilator patients by using the technique of rapid airway occlusion during constant flow inflation (Polese et al. 1991). This technique implies that flow is interrupted at the end of inspiration while pressure is kept constant during a period of time (pause time). The interrupter technique is only valid when the ventilator operates in a constant flow mode that means that flow is constant throughout inspiration. Resistance in mechanical ventilation describes the airflow condition during both inspiration and expiration. Resistance represents the flow-resistive elements of the respiratory system. It is expressed as a pressure variation over gas flow using the following general equation:

$$\text{Resistance} = \frac{\Delta \text{Pressure}}{\text{Flow}}$$

Fig. 11.11 In this loop airway pressure continues to increase beyond the zone of maximal compliance, and the inspiratory limb flattens into the zone of overdistension (dashed line). This portion of the curve represents alveolar overdistension and decreased compliance. The point at which this occurs is called the upper inflection point (UIP). The airway pressure at the upper inflection point identifies the pressure beyond which alveolar overdistension occurs



By substituting standard units, it becomes

$$\text{Resistance} = \frac{\text{cm H}_2\text{O}}{\text{ml} \cdot \text{s}^{-1}}$$

Airway resistance is affected by flow, tidal volume, and the network dimensions. The size of the endotracheal tube is an important element in gas flow through the breathing circuit and thus affects resistance. When delivering a set tidal volume at a set flow, smaller and longer tubes will produce larger resistance to gas flow.

When a ventilator operates in a constant flow mode, the resistive elements of the respiratory system/breathing circuit can be visualized and calculated with the pressure–time waveform (Fig. 11.12). The pressure–time waveform begins with an exponential rise to peak inspiratory pressure.

The first step is a function of flow and resistance during the initial portion of inspiration. The higher the step, the larger the resistance. The second portion of the waveform is a linear increase to peak inspiratory pressure and is a function of flow being constant throughout inspiration. This second portion represents the elastic properties of the respiratory system.

As peak inspiratory pressure is reached, a pause time or plateau is maintained, while pressure inside the airways and the breathing circuit

equilibrates at plateau pressure (P_{plat}). Flow then stops while pressure equilibrates.

Figure 11.12 is a pressure–time waveform from a constant flow mode of ventilation and illustrates various elements related to resistive and elastic properties of the respiratory system.

Inspiratory resistance is the difference between PIP and P_{plat} over flow value at PIP, as expressed by the following equation:

$$R_I = \frac{\text{PIP} - P_{\text{plat}}}{\text{PIF}}$$

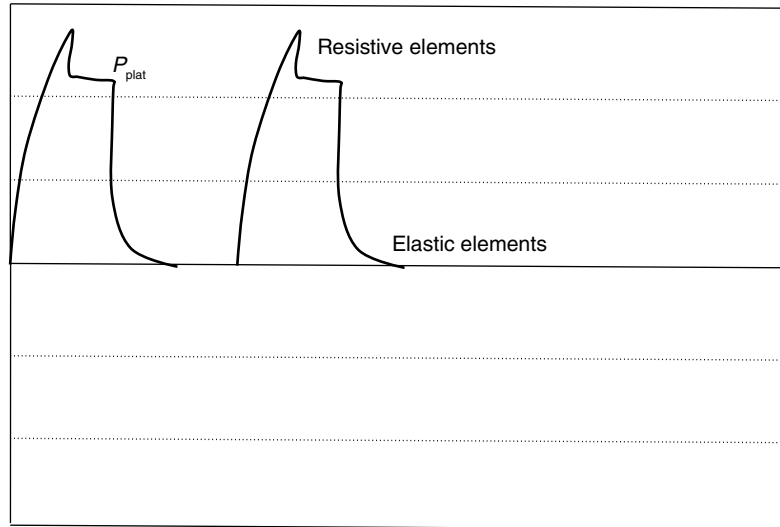
Expiratory resistance is the difference between P_{plat} and total PEEP over flow value at the onset of exhalation, as expressed by the following equation:

$$R_E = \frac{\text{PIP} - \text{PEEP}_{\text{TOT}}}{\text{Flow at onset of exhalation}}$$

11.5.7.4.1 Limitations

Specific measuring conditions must be met for a valid inspiratory and expiratory resistance value which includes a passive tidal volume (inspiration and expiration) and constant flow over a fixed inspiratory time for inspiratory resistance only; the P_{plat} must have an end-inspiratory pause of at least 1 s with a stable pressure within 0.5 cmH₂O over 2 readings at least 10 ms apart.

Fig. 11.12 When a ventilator operates in a constant flow mode, the resistive elements of the respiratory system/breathing circuit can be visualized and calculated with the pressure–time waveform



11.6 Respiratory Time Constants

11.6.1 Time Constants: Basic Meaning and Concepts of Intrapulmonary Pressure Equilibration

The time constant of the lung (TC) is a concept borrowed from electrical engineering that describes the phenomenon whereby a given percentage of a passively exhaled breath of air will require a constant amount of time to be exhaled regardless of the starting volume given constant lung mechanics. Exponential functions are often described with time constants, designated by the Greek letter τ (tau). The time constant characterizes the rate of variation of the function over a period of time. Short time constants imply a fast rate of change and, vice versa, long time constant implies a slow rate of change.

During quiet breathing, equilibration between alveolar and mouth pressures occur at both the end of expiration and the end of inspiration such that time constants of the respiratory units are relatively small (0.01 s). Therefore, during quiet breathing the change in volume divided by the change in pleural pressure is dynamic compliance of the respiratory system and is the same as the static compliance. In the normal lung, since the time constants are small and equilibration between alveolar and mouth pressure still occurs,

increases in breathing frequency to rates of 80/min do not affect the measured compliance. In contrast, in patients with peripheral airway disease, with more rapid breathing, the time constants of at least some of the respiratory units are increased so that equilibration between the alveolar and mouth pressure does not occur at either end-inspiration or end-expiration. Accordingly, the volume change with a given pleural pressure change falls with increasing respiratory rate, and the compliance is said to be frequency dependent (Woodcock et al. 1969).

Changes in dynamic compliance with increasing respiratory rate in patients with relatively normal expiratory flow rates may be marked. Woodcock et al. (1969) found that the dynamic compliance was reduced to less than 50 % of static compliance in mild asthmatics breathing at a respiratory frequency of 80/min. A large proportion of the decrease in dynamic compliance owes to the pendelluft effect where at times of zero flow at the mouth, air flows from one region to another. This mechanism is illustrated in Fig. 11.13. During inspiration, alveolus 1 fills more rapidly than alveolus 2 because of the increased airway resistance of the airways leading to alveolus 2 and hence its larger time constant. If the inspiratory time is short, alveolus 2 never becomes completely filled. Then on expiration, the pressure in alveolus 1 is higher than the pressure in alveolus 2 because of its larger volume; therefore, flow goes not only from

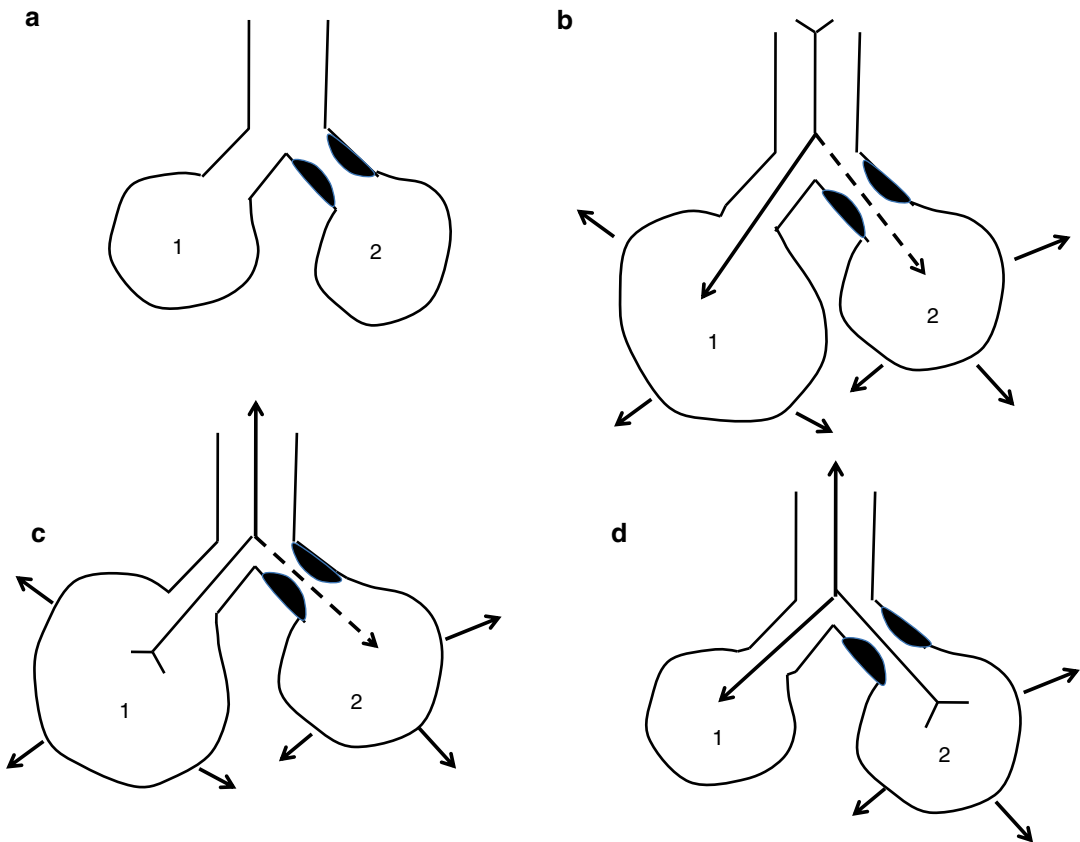


Fig. 11.13 Effects of uneven time constants on ventilation. The airway leading to unit 2 is partially obstructed and therefore unit 2 has a longer time constant. After a slow expiration (**a**), the units have the same size. With a rapid inspiration (**b**), unit 1 fills more than unit 2 because it has a faster time constant. Shortly after the start of a rapid expiration (**c**), air moves not only from unit 1 to the

airway opening but also from unit 1 to unit 2 because the pressure in unit 2 is less than pressure in unit 1. During the later phases of expiration (**d**), flow moves from unit 2 to unit 1. As the respiratory rate is progressively increased, the tidal volume of the abnormal region becomes smaller and smaller

alveolus 1 to the mouth but also from alveolus 1 to alveolus 2. The higher the frequency, the lower the tidal volume to the abnormal region.

Tests of dynamic compliance are sensitive indicators of peripheral airway disease. The time constants of the lung units distal to airway 2 mm in diameter are on the order of 0.01 s. Fourfold increase in some time constants is necessary to cause dynamic compliance to become frequency dependent.

Time constants of the respiratory units markedly influence the distribution of ventilation. A second factor that is influential is the regional differences in pleural pressures. Owing to the regional differences in pleural pressure, dependent parts of the lung are ventilated better. Other

factors that influence the distribution of ventilation are the interdependence that exists between adjacent lung units and the presence of collateral pathways for ventilation.

11.6.1.1 Concepts of Intrapulmonary Pressure Equilibration

A model can be constructed in which the alveoli are represented by an elastic sac and the intrathoracic airways by a compressible tube, both of which are enclosed within a pleural space. The concept of an equal pressure point (EPP) described by Mead is when sufficient expiratory effort is generated then the pleural pressure becomes positive, and in this situation the intrabronchial pressure at some point

along the airways is equal to the pleural pressure extrabronchial pressure. The EPP divides the airways into two components arranged in series with an upstream segment from the alveoli to the equal pressure point, where the distending pressure of the bronchi is positive, and a downstream segment from the EPP to the airway opening, where the distending pressure of the bronchi intrathoracic is negative. In these downstream segments collapse will occur during forced expiration.

There is no EPP when the pleural pressure is subatmospheric. However, when the pleural pressure becomes atmospheric, the EPP is at the airway opening. The EPP moves upstream as the pleural pressure becomes more positive. The alveolar pressure minus the pleural pressure represents the pressure drop from the alveolus to the EPP. This pressure represents the elastic recoil pressure of the lung. The resistance of the upstream segment is designated R_{us} . Therefore, flow is

$$\dot{V} = P_{st(L)} / R_{us}$$

$P_{st(L)}$ is constant at a constant lung volume. Thus, $\dot{V}$ can only increase if R_{us} decreases, which can be accomplished by moving the EPP upstream. The movement of the EPP upstream is caused by more and more effort until the pleural pressure reaches a level at which further increases in it do not lead to further increase in $\dot{V}$. This lack of change in flow is called $\dot{V}_{max}$ and corresponds to point on pressure–flow curve where the wave-form is flat.

$\dot{V}_{max}$ is dependent on two factors:

$$\dot{V}_{max} = P_{st(L)} / R_{us}$$

R_{us} is the resistance of the upstream segment and $P_{st(L)}$ being the recoil pressure of the lung. Thus, in reducing $\dot{V}_{max}$ a decrease in elastic recoil of the lung is just as important as is increased airway resistance.

Figure 11.14 represents a model described by Pride (Pride et al. 1967) where the airways are divided into two rigid tubes connected in series by a short segment of a collapsible tube. The airways are divided into an upstream segment between the alveoli and airways into an upstream

segment between the alveoli and the distal end of the collapsible segment to the airway opening. They defined the critical closing pressure of the collapsible segment (P'_{tm}) as the transmural pressure (P_{tm}), at which the segment collapsed. Thus, the transmural pressure, in this distensible object, is the pressure inside the wall minus the pressure outside the wall. The value of P'_{tm} represents the necessary distending pressure to maintain the collapsible segment patent. So this segment would be fully open when the distending pressure exceeds P'_{tm} and fully collapsed when P_{tm} fell below P'_{tm} . Calculation of the transmural pressure in the collapsible segment is

$$P_{tm} = P_A - (\dot{V} \times R_s) - P_{pl}$$

where R_s is the resistance of the segment upstream from the collapsible segment. Since

$$P_A = P_{st(L)} + P_{pl}$$

then

$$P_{tm} = P_{st(L)} - (\dot{V} \times R_s)$$

Therefore, as $\dot{V}$ increases, P_{tm} decreases. When $\dot{V}$ increases to a critical level ($\dot{V}_{max}$), P_{tm} drops to P'_{tm} . This is demonstrated in Fig. 11.14 where $P_{tm} = 6 - 6 = 0$ and it is assumed $P'_{tm} = 0$. If flow rates increase more, as seen in Fig. 11.14, the P_{tm} would fall below P'_{tm} and there would be no flow due to the collapse of the segment (Fig. 11.14d). However, in this situation the intrabronchial pressure becomes the same as the alveolar pressure, due to the absence of flow, and P_{tm} would exceed P'_{tm} and flow would resume. If the collapsible segment opens all the way, $\dot{V}$ again exceeds $\dot{V}_{max}$, P_{tm} falls below P'_{tm} and airflow ceases. Thus, the best way to explain this interrelationship is to consider the collapsible segment as a variable resistor illustrated in Fig. 11.14e, f. Partial collapse of the segment occurs when pleural pressure is reached to level necessary to cause collapse with P_{tm} equal to P'_{tm} . While pleural pressure increases further, there is a corresponding pressure drop across the collapsible segment. So as can be seen in Fig. 11.14b, e, f, once flow limitation is met, flow and intrabronchial pressure downstream do not change. If we examine this from our mathematical model, we recognize that flow limitation

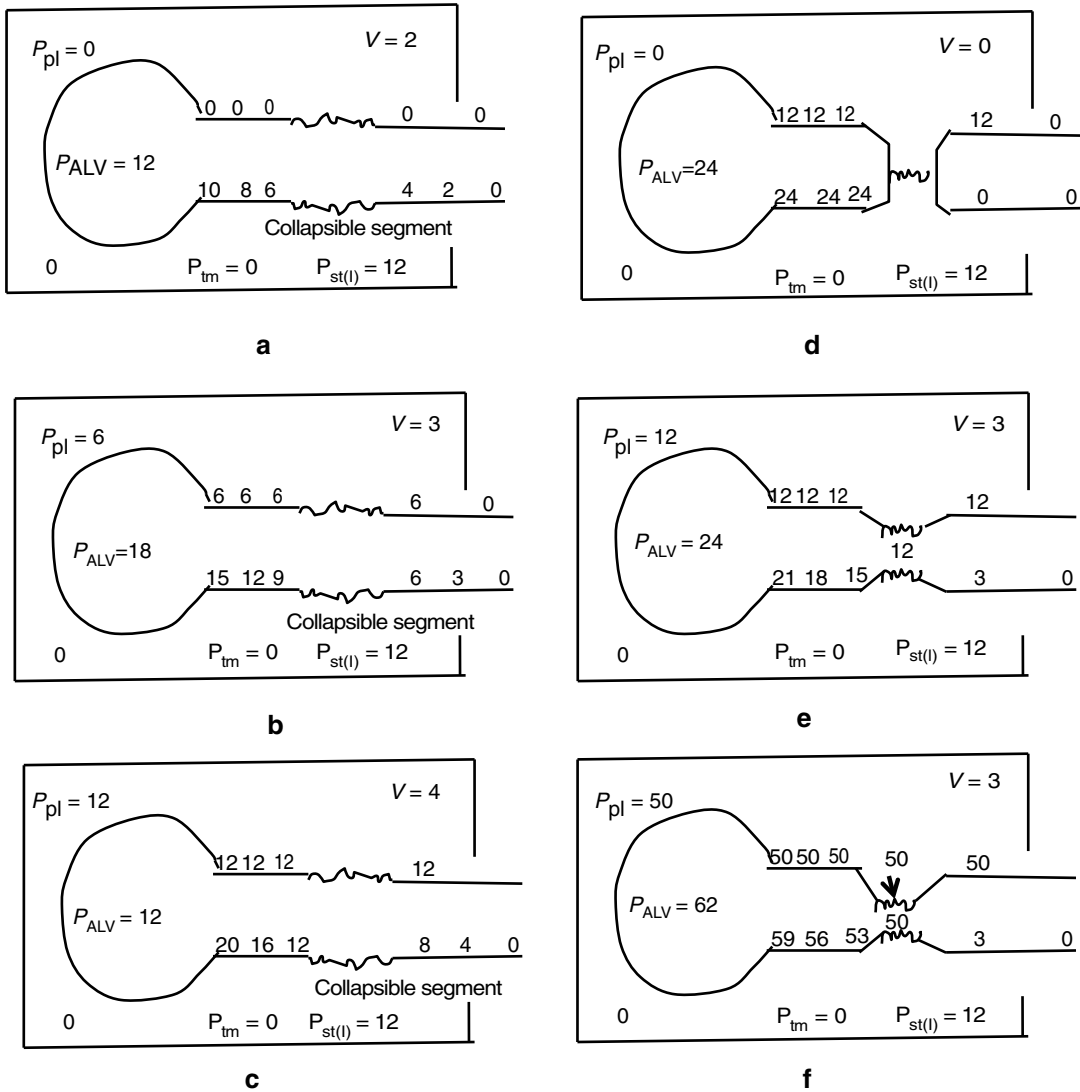


Fig. 11.14 A schematic representation of the collapsible-segment concept. In these diagrams the lung volume is that giving a $P_{st(l)}$ of 12 and it is assumed that P'_{tm} is zero. (a) Pressure along the airways when P_{tm} still exceeds P'_{tm} . There is no collapse. (b) Pressure along the airways when P_{tm} approaches P'_{tm} . Note that the flow rate increases from (a). (c) Pressures along the airways when pleural pressures are increased more. Note that P_{tm} at the collapsed segment is now $8 - 12 = -4$ which is below $P'_{tm} = 0$, so this higher flow is impossible since the collapsible segment must collapse. (d) Pressures along the airways when there

is no flow. Now $P_{tm} = 24 - 12 = 12$, so the airway must open. (e) Pressure along the airways when the collapsible segment is partially collapsed such that $P_{tm} = P'_{tm}$. (f) Pressures along the airways when the collapsible segment is partially collapsed such that $P_{tm} = P'_{tm}$. (f) Pressures along the airways when the alveolar pressure is raised much higher. Note that the collapsible segment is more collapsed than in (e) and that the flows in (b, e, and f) are also identical. The airway pressures downstream from the collapsible segment in (b, e, and f) are also identical

occurs when $P_{tm} = P'_{tm}$. If we substitute P_{tm} 's for P_{tm} in our previous equation, then

$$P'_{tm} = P_{st(l)} - \dot{V}_{max} \times R_s$$

or can be rewritten to calculate maximum flow as

$$\dot{V}_{max} = (P_{st(l)} - P'_{tm}) / R_s$$

Thus, $\dot{V}$ max depend upon three different factors: (1) the resistance of the upstream segment (R_s), (2) the elastic recoil of the lung ($R_{st(L)}$), and (3) the tendency of the airways to collapse (P'_{tm}). Clinical examples of this relationship with reduced flow rate during expiration can be seen in asthma with constriction of the bronchial smooth muscles increasing the tendency of the airways to collapse (P'_{tm}) and thereby reduce flow rates, and the lungs cannot empty to a lung volume below which P'_{tm} exceeds $P_{st(L)}$.

11.6.2 Measurement of the Time Constant

The pressure applied by the ventilator and the respiratory muscles is necessary to overcome the extrinsic and intrinsic forces on the lungs and chest wall during ventilation in intubated patients.

Theoretically, inspiratory volume production is active and can be forced by external pressure application; but since exhalation is passive, it cannot. Thus, time is required to empty the lungs and that time depends on the expiratory time constant.

Expiratory time constant is defined as the product of the total respiratory system compliance and the total expiratory resistance. While the former is determined by factors internal to the subject, the latter is the sum of airway resistance, any viscous tissues resistance, and externally applied resistance, such as valves and hoses in intubated patients. The calculation of the expiratory time constant requires knowledge about all of these elements and thus the measurement of flow and pressure at the airway opening.

The actual expiratory time constant can be calculated as (Brunner et al. 1995)

$$(R_{rs} + R_{ext}) \cdot C_{rs}$$

R_{rs} is the resistance of the respiratory system, R_{ext} the resistance of the expiratory valve and circuit, and C_{rs} the compliance of the total

respiratory system. The expiratory resistance of the ventilator, R_{ext} , can be measured separately by dividing the pressure drop with a flow rate directed through the expiratory valve and hoses: ($R_{ext} = \Delta P / \Delta V$ prime).

11.6.3 Simplified Approach (Analysis of the Flow–Time Curve and the Flow–Volume Loop)

11.6.3.1 Flow–Time Curve

In mechanical ventilation, for practical purposes, an event is considered complete after three time constants. For the adult respiratory system, the normal time constant is 0.79 s.

The actual value of one time constant is obtained through the product of compliance $\times$ resistance:

$$\tau = C \times R$$

$$\tau = \frac{\text{ml}}{\text{cm H}_2\text{O}} \times \frac{\text{cm H}_2\text{O}}{\text{ml} \cdot \text{s}^{-1}}$$

As an example, a system with a total lung/thorax static compliance of 60 ml/cm H₂O, an expiratory resistance of 0.13 cm H₂O/ml, and no auto-PEEP has a time constant τ of

$$\tau = C \times R$$

$$\tau = \frac{60 \text{ ml}}{\text{cm H}_2\text{O}} \times 0.13 \text{ cm H}_2\text{O} / \text{ml} / \text{s}$$

$$\tau = 0.78 \text{ s}$$

Figure 11.15 illustrates a flow–time waveform during a constant pressure mode of ventilation with a short and long time constant. In a decaying exponential function, a time constant of 0.78 s means that after one time constant (0.78 s) the value of the variable on the y-axis decreases to 37 % of its final value; after two time constants (1.56 s), it decreases to 13.5 % of its final value; and after three time constants (2.34 s), the value of the variable on the y-axis decreases to 5 % of its final value.

In this example of a flow–time waveform from a constant flow mode of ventilation (Fig. 11.16),

Fig. 11.15 Flow–time waveform from a constant pressure mode of ventilation. *A* represents an exponential function with a short time constant. *B* represents exponential function with a long time constant

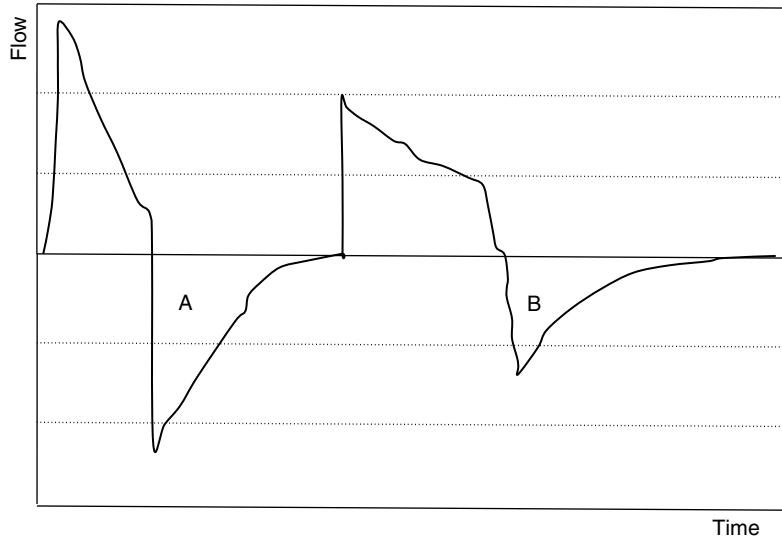
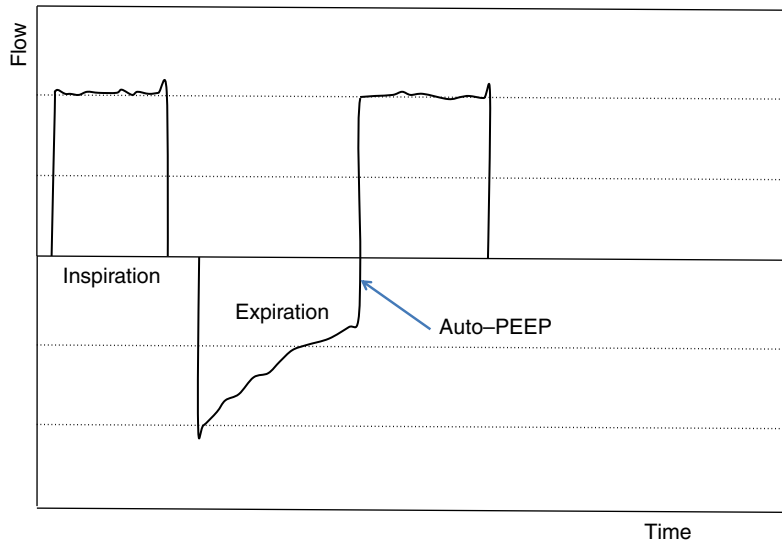


Fig. 11.16 Flow–time waveform from a constant flow mode of ventilation. Tracing reveals increased resistance with evidence seen with the linear decay during expiration with a slow decay to baseline with nonzero flow conditions at the end of expiration with evidence of auto-PEEP



if the expiratory time is shorter than 2.34 s (3×0.78), air trapping will be present, causing auto-PEEP.

To prevent auto-PEEP and air trapping, the expiratory time should always be longer than three time constants.

11.6.3.2 Flow–Volume Loop

The flow–volume loop (Fig. 11.17) has an inspiratory and expiratory phase. During the inspiratory phase, there is a rapid rise to peak inspiratory flow throughout inspiration with a rapid decay

from peak inspiratory flow to baseline. In expiration there again is a rapid decay to peak expiratory flow, and then the flow progressively returns to baseline. During a constant flow mode of ventilation, resistive changes are not reflected in the inspiratory profile. An airflow limitation that is reflective of resistive changes is associated with a convex (to the volume axis) shape of the second phase of the expiratory profile of the loop. These changes are reflective of dynamic changes and no static characteristics of the respiratory system can be described with a flow–volume loop.

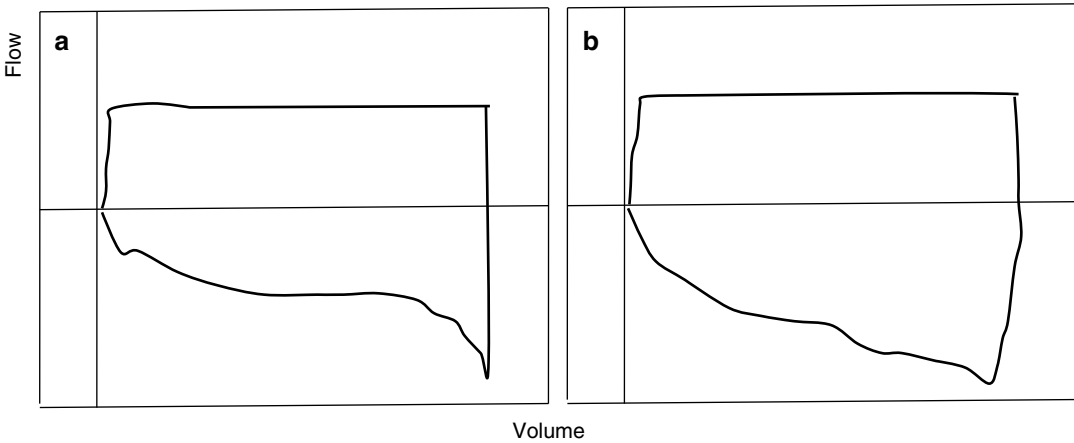


Fig. 11.17 Flow–volume loop from a constant flow mode of ventilation. Tracing (a) illustrates increased resistance and (b) normal resistance. In tracing (a) increased resistance can be seen with linear return to baseline

11.7 Lung Volume Measurements in the Ventilated Patient

11.7.1 Techniques and Methods

In order to use measurement of respiratory mechanics in clinical decision making for mechanically ventilated patients, some measurement of volume is required. Volume in mechanically ventilated patients can consist of the volume delivered by the ventilator or some measurement of the patient's actual lung volume. The discussion below will first discuss measurement of volume by the ventilator and on methods of measuring the patient's actual lung volumes.

11.7.1.1 Measurement of the Delivered Volume by the Mechanical Ventilator

Volume (V) can be obtained by numerically integrating flow ($\dot{V}$) by a computer. The trapezoidal rule is sufficient for virtually all respiratory applications, provided $\dot{V}$ is sampled rapidly enough (50 Hz or more). Thus, this integration can be accomplished when

$$V = V_0 + \sum_0^N \Delta V_i \quad \text{where} \quad \Delta V_i = \left(\frac{\dot{V}_i}{2} + \frac{\dot{V}_{i+1}}{2} \right) \delta t$$

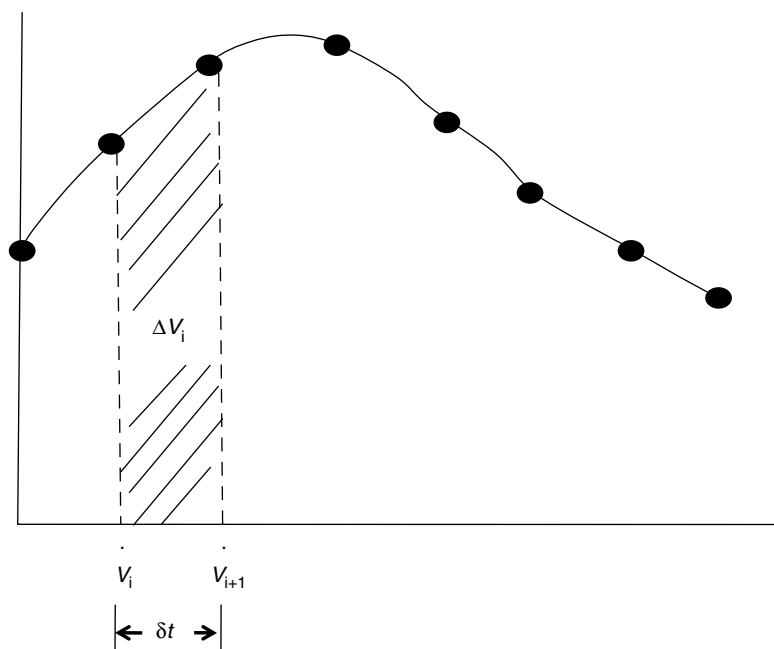
δt is the time interval between data samples and V_0 is the value of volume at the start of the integration process (Fig. 11.18).

Integration of flow invariably leads to a drift in the resulting volume signal. This can be due to a number of factors, including non-unit respiratory exchange ratio, differences in a temperature and humidity between inspired and expired gas, and slight errors in calibrating the zero flow point. Accurately accounting for all these effects is not practical, so one is left with having to remove volume drift in whatever way seems reasonable.

11.7.1.2 Measuring the Specific Lung Volume of the Patient

To measure specific lung volumes, a number of techniques have been used including CT measurements. Computed tomography (CT) can provide an accurate measurement of tissue mass and volume (Mull 1984). CT allows computation of both tissue mass and gas volume of the lung due to the fact that lung tissue has a physical density close to water density (Denison et al. 1986). This technique has been used by investigators to measure changes in EELV and to quantify alveolar recruitment both in an animal (Pelosi et al. 2001) and human (Gattinoni et al. 1988) studies. However, despite the fact that CT scanners are readily available to most clinicians, this measurement is limited by the risks associated with transporting such critically ill patients and its clinical relevance in

Fig. 11.18 The area under the *flow curve* is approximated as the sum of all the ΔV_i



patients with rapidly changing clinical status. An alternative technique has been to use a dilution technique based on dilution of tracer gases to measure the EELV in mechanically ventilated patients (Kendrick 1996). However, these techniques have been limited to experimental protocols due to the considerable expense required for the monitoring equipment. Simplified techniques have been proposed but require further validation to gain wide spread use (Patroniti et al. 2004).

11.7.2 Result Interpretation and 7.3 Limitations, Drawbacks, and Unknowns

During mechanical ventilation volume is not directly measured by the ventilator but is calculated from the flow signal. Any error in measurement of flow will decrease the accuracy of the measurement of the volume. There are numerous sources of error as it relates to the measurement of flow. For volume measurement to be accurate then all volume delivered to the patient has to be measured. Thus, the first source of error would be loss of volume within the ventilator circuit resulting from compression volume of the circuit. In the inflation phase, pressure rises within

the ventilator circuit causing elongation and distension of the tubing and compression of the gas within the circuit. The volume stored in the circuit never reaches the patient but is instead released through the exhalation valve and is measured with the exhaled gases from the patient. The magnitude of compression volume is determined by the volume within the ventilator, circuit, and humidifier. This volume loss theoretically can be affected by a number of factors, including temperature and humidity of the circuit, and patient factors such as changes in the patient's compliance and resistance. In a recent study, the reported differences in the measured compliance of the circuit by the manufacturer and those measured by the ventilator were between 37 and 65 % for the infant circuit and 13–23 % for the adult circuit (Heulitt et al. 2009a). Because this factor is collected at start-up of the ventilator and includes any compression volume in the ventilator and humidification system, this number will be higher. It was found that the compensation measured in the circuit and ventilator system was 51 and 18 % higher, respectively, than could be expected from the compression volume calculated using the compliance factor of the circuit alone. Thus, if only the circuit compliance factor is used, then the volume measured at expiration,

which accounts for both volume of the circuit and volume delivered to the patient, will be higher than the calculated effective volume.

Another potential source of error during the measurement of volume is the timing of the measurement of the flow. For accurate measurement of the flow, it should be begun at the beginning of the breath and ended when the system returns to baseline. To accurately measure the beginning of the breath, it should correspond to the time point when the initial flow crosses the zero line for flow signaling patient triggering or opening of the inspiratory valve in controlled breaths. Unfortunately, these two time points can correspond to times of high turbulence thus high signal noise. Thus, it is common for mechanical ventilator measuring algorithms to avoid these areas thus decreasing the potential accuracy of volume measurement.

Future Perspectives

There have been major advances in the availability of performing lung function tests in infants and children. However, the application of these tests to patients who are on mechanical ventilation continues to be limited outside of its use in research. Future direction has to expand our knowledge of the natural course of pulmonary involvement in infants and children and its implications on subsequent care. Currently infants and children who have a history of pulmonary insult comprise a difficult population and consume considerable resources and time to care for them. Our lack of understanding of the natural course of these patients disease process impacts our ability to perform measurements of respiratory mechanics because many of the assumptions we use in making measurements of lung volumes and mechanics may not be true. Future advances will require techniques that are reproducible and can easily be applied to clinically unstable patients. These new techniques have to be able to address the issue of

inaccuracies in displayed values of tidal volume, interactions between the ventilator and spontaneous breathing activity, and issues created by potential leak around the endotracheal tube. Some of these issues could be addressed, for example, by the use of cuffed endotracheal tubes that may pose very little risk to the patient outside of the neonatal period (Newth et al. 2004). Others will require better understanding of both the natural course of pulmonary development but also elucidation of the mechanism by which insults affect this development.

Essentials to Remember

- The respiratory system is not a linear system; resistance and compliance are not constants. They are dependent upon volume, volume history, and flow.
- A model of the respiratory system is considered passive because the lungs respond to forces external to the lungs.
- In order to overcome the impedance of the respiratory system and to allow gas flow to occur, work must be performed.
- The resistance to airflow in a tube depends on the type of flow, the dimensions of the tube, and the viscosity and density of the gas. Airflows through tubes can either be laminar or turbulent.
- The airway pressure is the force that the mechanical ventilator and patient apply on the respiratory system.
- Resistance during mechanical ventilation describes the airflow conditions during both inspiration and expiration. Resistance represents the flow-resistive elements of the respiratory system.
- The time constant characterizes the rate of variation of the function over a period of time. Short time constants imply a fast rate of change and, vice versa, long time constants imply a slow rate of change.

11.8 Respiratory System Pressure-Volume Curve

11.8.1 Static Pressure-Volume Curve

Peter A. Dargaville

Educational Aims

This chapter aims to give an understanding of:

- The methods of generation of static or quasistatic pressure-volume (*PV*) curves, including the associated methodological considerations and sources of error
- The important landmarks on the inflation and deflation limbs of the *PV* curve and their relationship to expansion and aeration of lung units
- The theoretical potential and clinical experience of using *PV* landmarks to guide PEEP setting in the diseased lung

11.8.1.1 Introduction

The pressure-volume (*PV*) behavior of the lung has been a subject of some fascination for pulmonary researchers and clinicians for nearly a century (Mead 1996). Perhaps equally fascinating is that, despite a large body of literature detailing the landmarks of the *PV* curve and their significance, the place of the *PV* curve as a tool to guide clinical management remains undecided (Dreyfuss and Saumon 2001; Terragni et al. 2003; Gattinoni et al. 2005; Maggiore et al. 2003; Harris 2005; Albaiceta et al. 2008; Blanch et al. 2009). This chapter will summarize current knowledge of static or quasistatic *PV* curves in mechanically ventilated subjects. The different methods of mapping the *PV* relationship will be outlined. The important landmarks of the *PV* curve and their lung morphological correlates will be identified and their relative value in guiding ventilator pressure settings discussed.

11.8.1.2 The “Static” Pressure-Volume Curve

11.8.1.2.1 Measurement of the Static *PV* Curve: Methods, Conditions, and Error Sources

11.8.1.2.1.1 Generation of a Pressure-Time Curve: The Basis of *PV* Mapping

A static *PV* curve describes the volumetric response of the lungs or the respiratory system to sequential transpulmonary pressure (P_{TP}) changes which generally take the lung from a point at or above elastic equilibrium volume to total lung capacity (TLC) and back. In some cases only a portion of the curve, usually the early part of the inflation limb, is mapped. Whether P_{TP} is generated via negative intrapleural pressure in a spontaneously breathing individual, or application of positive pressure at the airway opening, to eliminate resistive pressure drop, truly static *PV* mapping requires a period of equilibration at zero flow after each pressure step. Even with a long pause following each pressure alteration, as is achievable in the ex vivo lung or experimental animal, pressure rarely stabilizes completely (Fig. 11.19). In the ventilated human subject, the need for tidal ventilation to sustain life necessitates the use of shorter equilibration periods at each target pressure during *PV* curve tracing.

The following review of the methods used to obtain *PV* curves focuses on those that can be applied in ventilated human subjects.

Super-Syringe Technique

Application of positive pressure at the airway opening using a large graduated syringe (super syringe) is a time-honored method of generating *PV* curves in both experimental animals (Rimensberger et al. 1999) and ventilated adults with acute respiratory distress syndrome (ARDS) (Matamis et al. 1984; Gattinoni et al. 1987a). The syringe is connected directly to the endotracheal tube and the plunger moved in regular volume steps, with a pause of around 3 s after each. Once a predetermined peak airway pressure is reached (up to 40 cm H₂O in adults), the volume is withdrawn in the same way. The

Fig. 11.19 Pressure wave during *PV* curve mapping. Inflation and deflation pressure–time plots during *PV* curve mapping using the super-syringe method. Note the exponential pressure decay from initial pressure after each volume step. Pressure values used in the construction of the quasi-static *PV* curve are indicated by *open circles* (Redrawn from Harris (2005) with permission)

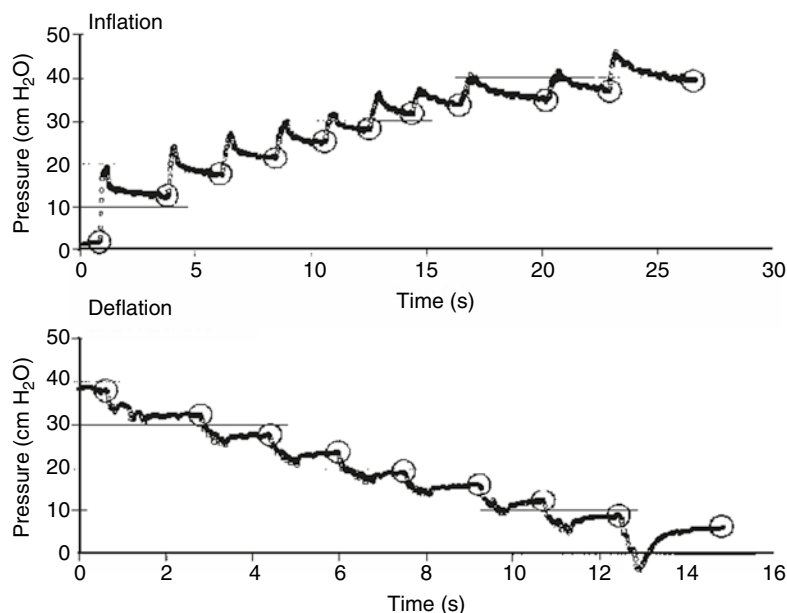
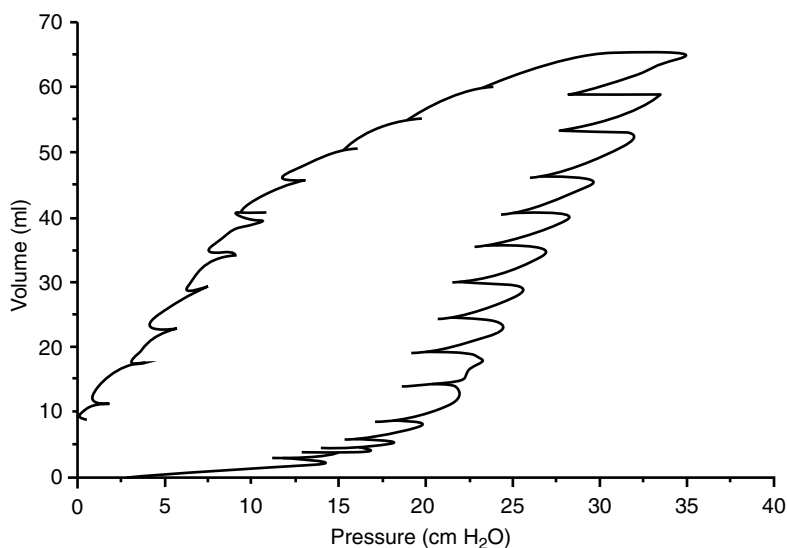


Fig. 11.20 Typical static *PV* curve. *PV* tracing obtained using a syringe technique in a ventilated rabbit after repeated saline lavage (Redrawn from Rimensberger et al. (1999) with permission)



entire *PV* curve (inflation and deflation) can be mapped in about 40–60 s (Figs. 11.19 and 11.20). The method has been performed in sedated and muscle-relaxed infants with respiratory distress syndrome (Pfenninger and Minder 1988).

At first glance, the super-syringe technique would appear to have the advantage of accurate measurement of gas volume changes at the airway opening, but several sources of error limit the accuracy of the volume measurements, related in part to the use of cold dry gas (see below). The technique has the additional disadvantage of

need for disconnection from ventilation, which for subjects with serious lung disease inevitably leads to destabilization (Mehta et al. 2003). For this reason, the super-syringe technique has largely been abandoned in clinical practice.

CPAP Steps Technique

An alternative to the super-syringe method is the CPAP steps technique, where with the ventilator in CPAP mode, the airway pressure is manually adjusted in 5 cm H₂O steps, up to a predetermined peak value and back, with a pause after

each pressure change until zero flow conditions are reached (Albaiceta et al. 2003; Albaiceta et al. 2004). The technique is attractive in that disconnection from the ventilator is not required, and the inflation-deflation maneuver is completed with warmed humidified gas. At least in experimental animals, the resultant *PV* curves are very similar to those obtained using a super syringe (Albaiceta et al. 2003). In ventilated humans, the technique has been used to map the inflation and deflation limbs separately, with each maneuver lasting around 50 s (Albaiceta et al. 2004).

Multiple Occlusion Technique

Static *PV* curves can also be generated using the multiple occlusion technique, in which repeated periodic interruptions to tidal breathing at varying tidal volumes and rates are performed at end-inspiration, with recording in each case of tidal volume and plateau pressure (Levy et al. 1989). The method has the advantage of not requiring disconnection from the ventilator and appears comparable with a super-syringe technique in identifying *PV* curve landmarks (Mehta et al. 2003). In common with other static methods, accurate *PV* points can only be obtained if there is no tube leak and no spontaneous breaths during the measurement. The multiple occlusion method can take up to 15 min to perform, making it somewhat impractical in ventilated subjects with lung disease. A simplified version of the method, finding volume during an inspiratory and expiratory hold, has been used in neonates on conventional and high-frequency ventilation (Pfenninger and Minder 1988).

Constant Flow Methods

An alternative to the “static” methods in which periods of zero flow at the airway opening are required for accurate *PV* mapping is to inflate and deflate the lungs using a constant gas flow and a steady change in airway pressure. The result is a “quasistatic” *PV* curve in which resistive pressure drop occurs, but its value is minimal at low flow rates (<10 l/min), and thus, the *PV* curve slope and landmarks are very similar to those obtained by static methods (Lu et al. 1999). At a higher flow rate (15 l/min), the inflation limb of the curve is shifted considerably to the right (Servillo et al. 1997). At an early stage this

approach was applied in newborn infants with respiratory distress syndrome, using a specialized inflating device in which constant flow was used to inflate the lung over 20–30 s (Mathe et al. 1987). Further evaluation of the low-flow technique used ventilators in volume control mode, delivering a fixed volume over the longest inspiratory time the ventilator allowed (<10 s) (Lu et al. 1999; Servillo et al. 1997). More recently, purpose-built software within several commercially available ventilators now allows this maneuver to be performed automatically over a longer time period (15–20 s), with options to vary the gas flow, the rate of pressure change, and the peak pressure (Macnaughton 2006).

PV Curves During High-Frequency

Oscillatory Ventilation

During high-frequency oscillatory ventilation (HFOV), it is possible to map the *PV* relationship with timed adjustments in mean airway pressure (P_{aw}), most effectively done in a sedated, muscle-relaxed individual. Volume changes have been measured with computed tomography (Luecke et al. 2003; Pellicano et al. 2009) and respiratory inductance plethysmography (RIP) (Brazelton et al. 2001; Tingay et al. 2006). When compared to a static *PV* curve, that obtained with slow HFOV steps achieves higher lung volume related to greater time-dependent recruitment and less hysteresis (Luecke et al. 2003). As a result the features of the *PV* curve may be less conspicuous (Luecke et al. 2003), although in a study of ventilated human infants, the *PV* curve mapped during HFOV had a characteristic shape, with readily identifiable landmarks particularly on the deflation limb (Fig. 11.21) (Tingay et al. 2006; Miedema et al. 2011).

Stepwise PEEP Maneuver

A form of *PV* curve can also be traced during conventional ventilation using stepwise alterations in PEEP with the ventilator in either pressure or volume control mode (Meier et al. 2008; Dargaville et al. 2010). The *PV* curve is drawn so as to connect the end-expiratory pressure–volume points for the last tidal breath at each PEEP step (Fig. 11.22). Although the period of equilibrium at end-expiration is brief, the *PV* curves obtained

with this method show the expected landmarks (Dargaville et al. 2010). No formal comparison with other techniques of *PV* mapping has been published to date.

11.8.1.2.1.2 Measurement of Lung Volume During *PV* Maneuvers

After the choice of method for generating the pressure sequence, the second major consideration

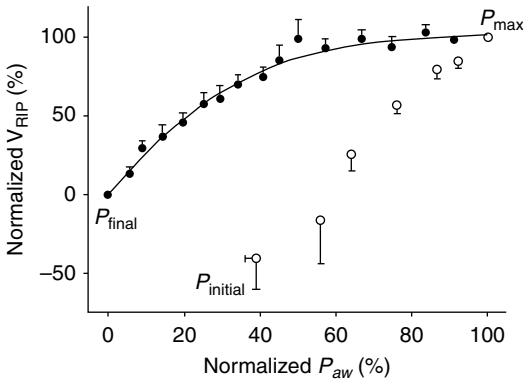


Fig. 11.21 *PV* curve during HFOV. Aggregate *PV* curve data from 12 muscle-relaxed infants on HFOV, with volume (measured by respiratory inductance plethysmography) normalized to total lung capacity (100 %) and deflation closing volume (0 %) and pressure normalized to the pressure values at these volume extremes ($P_{\max}$, P_{final}). Starting pressure (P_{initial}) was the P_{aw} in clinical use at the commencement of *PV* mapping (Reproduced from Tingay et al. (2006) with permission)

in *PV* curve mapping is the measurement of change in lung volume, which can be difficult, if not impossible, to perform directly in ventilated patients with lung disease. A number of different methods have been used, each with its own advantages, limitations, and sources of error.

Super-Syringe Method

Use of a graduated syringe would at first glance suggest highly accurate measurement of gas volume entering and leaving the lung. Several important sources of error are recognized with this method, which in sum tend to result in an unrecovered volume of gas during an inflation-deflation maneuver that may be falsely interpreted as hysteresis (Gattinoni et al. 1987b; Dall'Ava-Santucci et al. 1988). The first is the alteration in volume that occurs when cold, dry gas in a syringe is warmed to body temperature and saturated with water vapor. This effect is unique to the super-syringe technique, with a largely predictable error that can be corrected for (Gattinoni et al. 1987b). The second is gas compression occurring during inflation with higher airway pressures, an error common to all methods employing positive pressure at the airway opening to obtain a *PV* curve, for which there is a recognized correction factor (Downie et al. 2004). The third is the imbalance between oxygen uptake from, and CO_2 entry into, the lung,

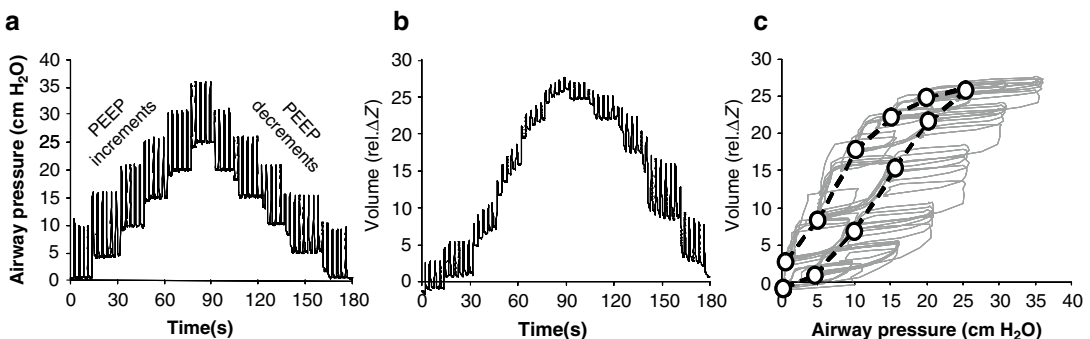


Fig. 11.22 *PV* curve using a stepwise PEEP maneuver. *PV* curve during PEEP increments and decrements in a mechanically ventilated piglet after repeated saline lavage followed by surfactant therapy. Panel (a) Pressure–time curve during pressure control ventilation with delta pressure held at 10 cm H_2O . Each PEEP level is held for approximately 15 s. Panel (b) Resultant volume–time

curve, with lung volume plotted as relative impedance change (rel. ΔZ) in arbitrary units. Panel (c) *PV* waveform (in grey), end-expiratory pressure–volume points for the final breath at each PEEP level (black circles) and the *PV* curve constructed from these points (dashed line) (Redrawn in part from Dargaville et al. (2010) with permission)

which leads to a loss of volume of delivered gas that is time dependent. This error is common to all methods of *PV* curve mapping and can be minimized to some degree by ventilation with room air prior to the measurement. The error can also be corrected for by timing the maneuver and using an estimate of the rate of oxygen consumption and the respiratory quotient (Bates et al. 1996).

Ventilator Techniques

Volume measurement during ventilator-driven *PV* curve mapping remains problematic. An integrated volume signal derived from a pneumotachograph placed at the airway opening inevitably shows a volume drift which has several causes, is not predictable, and is extremely difficult to correct for (Bates et al. 1996). Streaming of exhaled gas via a spirometer overcomes this problem, but this alternative is rarely available at the bedside.

CT Imaging

As noted below, measurement of gas volume changes using CT imaging has been the source of a great deal of information about the *PV* curve and its landmarks. CT scans have the advantage of separate estimation of volume change related to recruitment in non-aerated regions and volume accretion in previously aerated regions. Whole lung CT images give accurate quantitative measures of gas volume changes during a *PV* maneuver (Rouby et al. 2003). Most usually, however, only one or at best several CT slices can be taken at each pressure step (Albaiceta et al. 2004), which may not be representative of the whole lung (Lu et al. 2001). Use of CT imaging for tracing *PV* curves in clinical practice is also limited by the need for patient transfer to the CT suite and concerns over radiation exposure.

Respiratory Inductance Plethysmography (RIP)

This technique, discussed in detail elsewhere in this text, has been used to measure volume change during *PV* maneuvers in ventilated adults (Nunes et al. 2004) and neonates (Tingay et al. 2006) with lung disease and has the distinct advantage of being continuously available at the bedside in the intensive care unit. Calibration of the RIP voltage

change to a known volume is possible, but may not be accurate when taken to the extremes of volume during generation of a *PV* curve. Another potential source of error relates to shifts in blood volume that occur during tracing of an entire *PV* curve (Gattinoni et al. 2005), which will have the effect of exaggerating the degree of hysteresis. This effect may account in part for differences in TLC and deflation limb values seen when volume measurement using uncalibrated RIP is compared with values obtained using the super-syringe method (Brazelton et al. 2001).

11.8.1.2.1.3 Construction of the *PV* Curve

An additional potential source of error is the presence of endotracheal tube leak, which will lead to inaccuracies in the volume measurement in the super-syringe technique and also in methods requiring calibration with a known volume delivered at the airway opening. For this reason a cuffed tube is essential to accurately map the *PV* relationship; for neonates the alternative of a tight-fitting tube may be sufficient (Pfenninger and Minder 1988). Using an automated low-flow *PV* mapping system, it may be possible to overcome the potential error in identification of the lower inflection point by increasing flow rate (Turner et al. 2009), but doing so increases the error related to resistive pressure drop (Blanch et al. 2009).

11.8.1.2.2 Reproducibility of *PV* Curves

When generated using a consistent technique, *PV* curves in a ventilated subject are highly reproducible, with a considerable degree of overlap in *PV* points and peak volume measurements (Matamis et al. 1984; Mehta et al. 2003). Consistency of interpretation of the *PV* curve once drawn has been more problematic, in part related to discrepant definitions of key landmarks (Harris 2005), in particular the lower inflection point (LIP), also known as the lower corner pressure, or P_{flex} . A significant degree of intraobserver error in identification of LIP has been noted by some investigators (Harris et al. 2000), although not others (Mehta et al. 2003), potentially limiting the value of *PV* curve generation in guiding mechanical ventilation (see below).

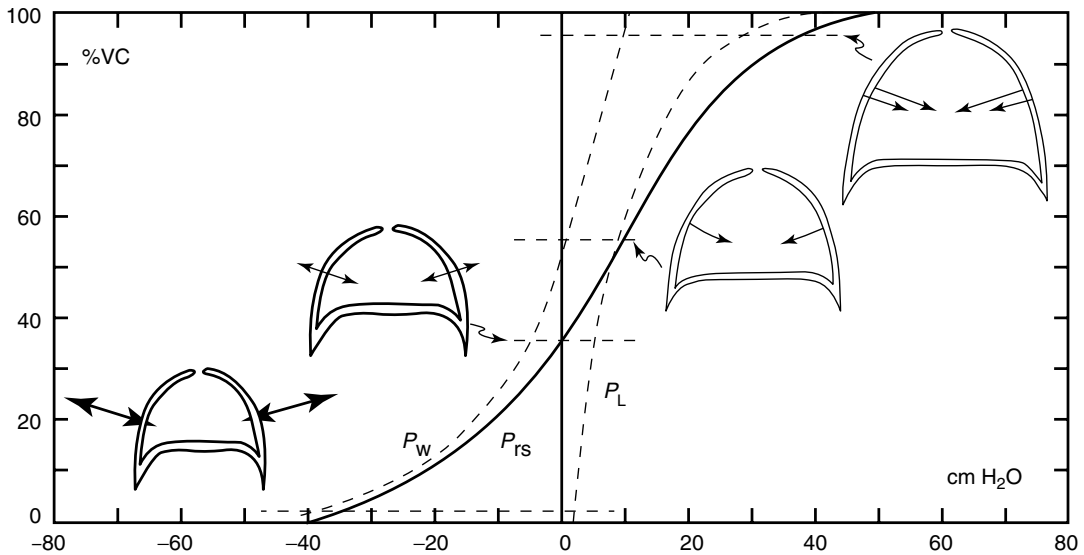


Fig. 11.23 *PV* curves of the lung, chest wall, and respiratory system. The *PV* curve of the respiratory system (P_{rs}) in a healthy adult (solid line) which is the sum of the curves of the lung (P_L) and chest wall (P_w) (both dashed lines). Functional residual capacity (FRC) occurs where the lung elastic recoil favoring collapse (inward arrows) is

balanced by the chest wall elastic recoil favoring expansion (arrows out). Note that the chest wall contributes much of the curvature below FRC, whereas the lung contributes most to the curvature above FRC. %VC = % vital capacity (From Agostini and Hyatt (1986) with permission)

11.8.1.2.2.1 Compartments Contributing to the Shape of the *PV* Curve

In a ventilated subject, the respiratory system *PV* curve constructed with pressure measurements from the airway opening (P_{ao}) is a composite of the *PV* relationship of the lungs and that of the chest wall and diaphragm (Agostini and Hyatt 1986). These can be separately drawn if a measurement of pleural pressure (P_{pl}) is made; for this purpose esophageal manometry is normally used. The *PV* curve of the lung can be drawn as volume change versus transpulmonary pressure (P_{tp} , where $P_{tp} = P_{ao} - P_{pl}$) and that of the chest wall as volume change versus P_{pl} (Fig. 11.23). Obesity and intra-abdominal sepsis, by virtue of their effects on the mechanics of the diaphragm and chest wall, demonstrably alter the *PV* relationship of the respiratory system (Pelosi et al. 1996; Ranieri et al. 1997), with morbid obesity also affecting lung compliance (Pelosi et al. 1996).

Leaving aside the contribution of the chest wall, the *PV* curve of the lung is the summation of the volumetric behavior of millions of alveoli and, as described in the next section, reflects both

isotropic volume change and recruitment/derecruitment, with regional inhomogeneities related to both the disease process and the effect of gravity.

11.8.1.2.3 The Inflation and Deflation *PV* Curves

11.8.1.2.3.1 Features of the *PV* Curve

The complete *PV* curve has inflation and deflation limbs, which may in some instances be traced separately. The shape of each limb and their identifiable landmarks have been long studied with the hope of yielding insights into the underlying anatomical and physiological disturbances of the diseased lung.

The inflation limb of the *PV* curve has a generally sigmoidal shape, less apparent in the healthy lung (Fig. 11.24) or where PEEP is applied during the maneuver (Maggiore et al. 2001; Ingimarsson et al. 2001). Several key landmarks of the inflation limb are apparent in the injured lung (Fig. 11.24). The LIP is located within the concavity at the lower end of the inflation limb, and has several definitions, directed toward identification of the point of maximum

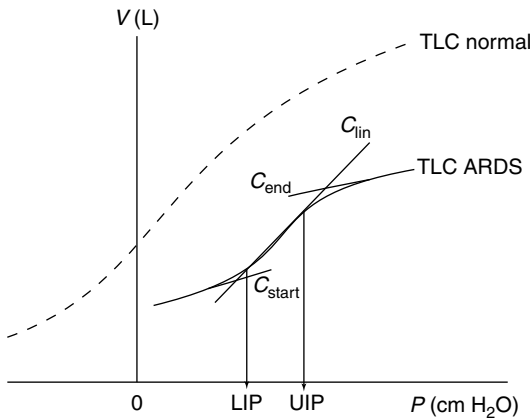


Fig. 11.24 *PV* curve inflation limb in the health and diseased lung. Inflation curve of a normal subject (*dashed line*) and a patient with ARDS (*solid line*). Note lower TLC in ARDS. *LIP* lower inflection point, *UIP* upper inflection point, C_{start} chord compliance below *LIP*, C_{lin} compliance in the linear region of the inflation limb, C_{end} compliance above *UIP* (Redrawn from Harris (2005) with permission)

concavity or most abrupt change in slope. It is not in actuality a true inflection point, which is a point on a curve at which concavity changes to convexity (or vice versa), and the second derivative changes sign. Below *LIP*, volume of the diseased lung changes little with pressure increments, and thus compliance is low. Above *LIP*, a relatively linear region of the inflation limb, with higher chord compliance, is seen (Fig. 11.24). As lung volume further increases, convexity of the upper end of the inflation limb is noted, beyond which volume proceeds asymptotically to *TLC*. The point of maximum convexity is known as the upper inflection point (*UIP*) (Fig. 11.24) and is not always demonstrable depending on the technique, the disease state, and the maximum pressure applied.

The deflation limb of the *PV* curve is less regularly sigmoidal in shape, having only an upper curvature apparent in most instances, within which a point of maximal curvature (*PMC*) is identifiable (Fig. 11.24). Below *PMC*, the deflation limb is generally linear.

When mapped together, the inflation and deflation limbs most usually have different trajectories, reflecting hysteresis within the respiratory system. Hysteresis can be defined as that

property of a mechanical system whereby different behavior is exhibited as a force is applied and then withdrawn. It may reflect unrecoverable energy or simply a delay in recovery of input energy, in either case indicative of an imperfect elastic system (Harris 2005). Many factors contribute to hysteresis under differing conditions (Harris 2005), with the most important being the elastic recoil generated by surface forces at the air–liquid interface associated with the alveolar lining layer (Radford 1964) and variable contributions made by lung tissue and chest wall hysteresis (Harris 2005; Albaiceta et al. 2008).

11.8.1.2.3.2 Anatomical and Physiological Correlates of *PV* Curve Landmarks and Hysteresis

Clinical and experimental studies have given insight into the relationships between *PV* curve landmarks and the anatomical and physiological state of the diseased lung. In particular, changes in lung aeration and recruitment at *LIP* and *UIP*, and on the deflation limb at the *PMC*, have been studied using computed tomography (CT), electrical impedance tomography (EIT), and confocal microscopy.

CT imaging in particular allows differentiation between isotropic aeration (increase in gas volume of open lung units) and recruitment (aeration of previously non-aerated areas). The inflation limb has been proposed to be a summation of the aeration and recruitment curves for all lung units, and the morphological changes in the diseased lung at the *LIP* and *UIP* have been identified using CT imaging (Fig. 11.25) (Albaiceta et al. 2004; Vieira et al. 1999; Jonson et al. 1999; Pelosi et al. 2001; Crotti et al. 2001). Below *LIP*, much non-aerated lung tissue is evident, very little recruitment occurs, the volume change that occurs is largely isotropic, and chord compliance is low. At *LIP*, significant recruitment of non-aerated lung begins, and, contrary to previously held tenets, above *LIP* recruitment continues as the linear portion of the inflation limb is traversed (Fig. 11.25) (Jonson et al. 1999). CT imaging in both experimental animals (Pelosi et al. 2001) and ventilated humans with lung injury (Crotti et al. 2001) indicates an approximately normal

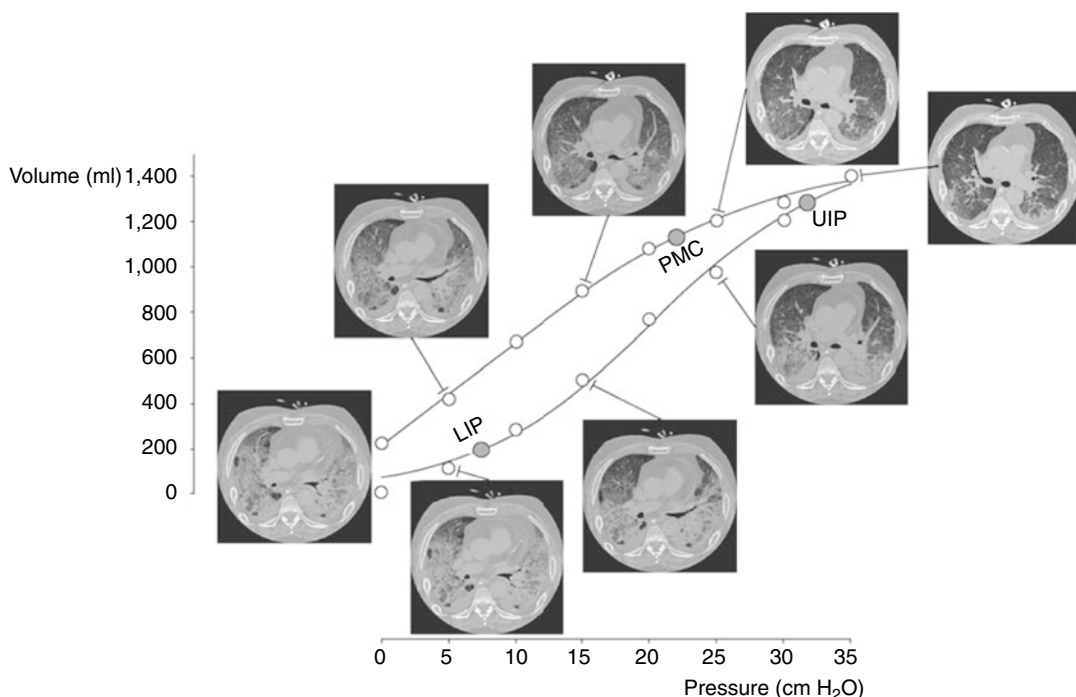


Fig. 11.25 *PV* curve landmarks and their relationship to recruitment and aeration in the diseased lung. *PV* curve traced under static conditions and corresponding axial computed tomographic images in a patient with acute respiratory distress syndrome (ARDS). On the inflation limb, recruitment (i.e., reduction in non-aerated lung) only begins after traversing the lower inflection point (*LIP*) and continues to and beyond the upper inflection

point (*UIP*). Increase in aeration of open lung regions proceeds throughout the inflation limb. On the deflation limb, derecruitment only starts below the point of maximum curvature (*PMC*) and progresses thereafter. Loss of volume in aerated regions occurs throughout the deflation limb (Reproduced from Albaiceta et al. (2008) with permission)

distribution of opening pressures of non-aerated lung units during inflation. The cumulative accretion of volume within such units over the pressure trajectory of the inflation limb (i.e., the integral of the normal distribution) gives a sigmoid curve and lends to the inflation limb its characteristic shape (Venegas et al. 1998).

Recruitment of non-aerated lung units diminishes at or near *UIP*, beyond which isotropic volume change is hampered by increasing lung strain. With the application of very high recruitment pressures, some lung units are noted to open above *UIP* (Borges et al. 2006).

At the top of the deflation limb, aerated lung units remain open with initial pressure decrements from *TLC*. At *PMC*, derecruitment is seen to begin (Fig. 11.25) (Albaiceta et al. 2004) and continues as the deflation limb is traversed (Maggiore et al. 2001), again with an apparently

normal distribution of closing pressures within the population of unstable units destined to collapse (Pelosi et al. 2001; Crotti et al. 2001). Onset of derecruitment on the deflation limb is not predictable from inflation limb *LIP* (Albaiceta et al. 2004; Crotti et al. 2001).

In parallel with the clinical and experimental studies using CT scanning, other modes of lung imaging, as well as measures of lung mechanics, have been used to examine the relationships between *PV* curve landmarks and lung inflation/aeration. Use of in vivo microscopy in the rat model of ARDS has allowed confirmation both of the phenomenon of recruitment along the entire inflation limb and the lack of prediction of derecruitment from inflation limb *LIP* (Dirocco et al. 2007). Onset of recruitment and derecruitment during the *PV* cycle has been estimated using both electrical impedance tomography

(Dargaville et al. 2010; Costa et al. 2009) and pneumotachography (Rimensberger et al. 1999; Ingimarsson et al. 2001), with again no clear relationship between derecruitment and LIP.

11.8.1.2.3.3 Modeling of the Inflation and Deflation Curves

Given on the one hand the potential for *PV* curves to give information which may aid in delivering mechanical ventilation and on the other the difficulties associated with generating entire *PV* curves and identifying landmarks on them, several approaches to modeling of the volumetric behavior of the lung have been pursued. Various sigmoidal functions have been reported to correlate well with clinical data, of which that of Venegas and coworkers (Venegas et al. 1998) has been most widely applied (Fig. 11.26a). This four-parameter sigmoidal equation uses variables related to *PV* curve landmarks, centered around the true inflection point, which is identifiable in most *PV* curves and of clinical significance. Hysteresis in this model can be introduced by using a different value for the inflection point on

the inflation and deflation limbs. This model has been seen to fit well with the *PV* curves of ventilated adults with ARDS (Pereira et al. 2003) as well as ventilated infants on HFOV (Tingay et al. 2006). A more fundamental approach has been taken in other studies, in which the cumulative volume of thousands of theoretical lung units is calculated as pressure is projected to and from TLC (Hickling 2001; Bates and Irvin 2002). In both models, the volume of each individual unit (once open) is derived from the exponential relationship between applied pressure and resultant lung volume established by Salazar and Knowles (1964). For the model of (Hickling 2001), the lung units have normally distributed opening and closing pressures and an array of different superimposed pressures. For that of Bates and Irvin (Bates and Irvin 2002), opening and closing pressures are assumed to be equal, but the rates of opening and closing differ for each unit, introducing time dependence as a factor contributing to the shape of the *PV* relationship. Each of these models produces *PV* curves with plausible inflation and deflation limbs (Fig. 11.26b, c).

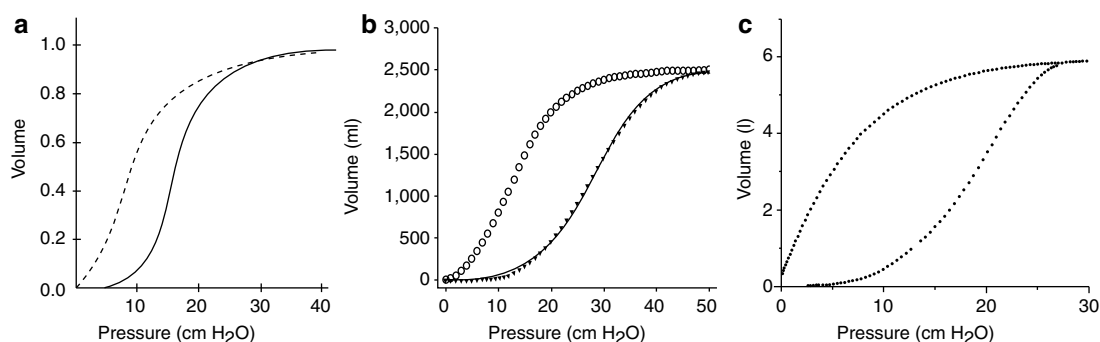


Fig. 11.26 *PV* curve modeling. Theoretical *PV* curves drawn using mathematical modeling, based around parameters of global lung function (panel **a**), or summing the volumetric behavior of clusters of individual lung units (panels **b**, **c**). In each case the lung is assumed to have been inflated from a degassed state. Panel (**a**): Sigmoidal functions representing the inflation and deflation limbs of a *PV* curve. In the example shown, the true inflection point (see text) was set to 15 cm H₂O for inflation and 5 cm H₂O for deflation (Reproduced from Venegas et al. (1998) with permission). Panel **b**: Inflation and deflation *PV* curves representing the cumulative sum of the volume of 27,000 individual units with superimposed pressure ranging between 0 and 14.5 cm H₂O

(equally distributed), threshold opening pressures between 0 and 40 cm H₂O (normally distributed), closing pressure 0 for all units, and the volume of open lung units determined from the equation of Salazar and Knowles (1964) with half-opening pressure=4.9 (Redrawn from Hickling (2001) with permission). Panel **c**: Inflation and deflation *PV* curves representing the cumulative sum of the modeled volumetric behavior of 5,000 individual units, with opening and closing pressures identical for each unit and normally distributed, time-dependent opening and closing, and the volume of open lung units determined from the Salazar–Knowles equation with half-opening pressure=4.9 (Redrawn from Bates and Irvin (2002) with permission)

11.8.1.2.4 Interpretation and Clinical Implication of the Static *PV* Curve

Spurred by the finding of Suter et al. (1975) that lung mechanics could guide PEEP setting for the ARDS lung, a legion of investigators have pursued the possibility that the static *PV* curve could be a bedside tool to assist ventilatory management, in particular PEEP setting. Clinical studies have largely been conducted in adult subjects with ARDS, with few reports of systematic evaluation of *PV* curves in ventilated infants and children. The findings of adult studies, and the laboratory work in experimental animals, certainly can be applied to the pediatric population.

LIP on the inflation limb of the *PV* curve has been the obvious starting point for clinicians looking for tools to assist in optimizing ventilation. Presence of a prominent curvature around LIP, with a significant increase in compliance from C_{start} to C_{lin} (Fig. 11.24), has been found to be indicative of the potential for recruitment (Vieira et al. 1999), which in turn predicts response to PEEP (Gattinoni et al. 2006). Further, where lung and chest wall *PV* curves are separately generated, the presence of an identifiable LIP on lung *PV* curve predicts response to PEEP (Mergoni et al. 1997).

Although laboratory studies confirm the presence of LIP in animal models of full-term (Monkman et al. 2004) and preterm (Ingimarsson et al. 2001) neonatal lung disease, few studies report the identification of LIP in ventilated infants and children (Pfenninger and Minder 1988; Mathe et al. 1987). Mathe and coworkers (1987) found concavity of the early part of the inflation limb with a recognizable LIP in each of 30 ventilated infants with respiratory distress syndrome. A further study in preterm infants identified a sigmoidal inflation limb in 6 out of 8 infants, but LIP was not used for PEEP optimization (Pfenninger and Minder 1988).

Until the morphological correlates of LIP were delineated (see above), this landmark was used in setting PEEP to achieve and maintain adequate lung recruitment. The strategy of setting PEEP above LIP (in conjunction with lung-protective

tidal volumes) was tested in several randomized controlled trials in adults with ARDS (Amato et al. 1998; Ranieri et al. 1999; Villar et al. 2006), each of which produced positive results compared with standard ventilatory management. In ventilated preterm infants, targeting PEEP to LIP was found to produce better oxygenation compared with an empirical approach to PEEP setting (Mathe et al. 1987). Recent evidence pointing to a lack of correlation between onset of derecruitment and LIP has however dampened the enthusiasm for this approach. The physiological incongruity of using an inspiratory curve landmark indicative of alveolar opening to set a pressure to prevent alveolar closure in the expiratory phase has been acknowledged (Maggiore et al. 2003).

The concept that deflation limb PMC might guide optimal PEEP has gained momentum over the past decade, based on both a theoretical consideration of optimal lung mechanics in the diseased lung (Hickling 2001) and the seminal observations of Rimensberger et al. (1999) demonstrating that tidal ventilation could be applied on or near the deflation limb of the *PV* curve after lung recruitment. The latter study noted in a lavage model of lung injury that optimal PEEP, at which lung volume and gas exchange were stable, was somewhat below PMC and well below LIP (Rimensberger et al. 1999). This is, in part, a reflection of the nature of the lung injury model – a highly recruitable lung that demonstrates marked hysteresis and considerable alveolar stability once recruited, meaning that deflation limb PMC can be well below LIP. Other laboratory (Takeuchi et al. 2002; Caramaz et al. 2009) and clinical (Harris et al. 2000; Crotti et al. 2001; Albaiceta et al. 2005) investigations have found PMC to be well above LIP, with as a consequence considerably higher PEEP if set at PMC. Experimentally this has been found to increase alveolar dead space (Takeuchi et al. 2002) and clinically to produce lung overdistension (Albaiceta et al. 2005), observations which may explain the lack of effect on ventilator days of a high PEEP approach (with tidal volume 6 ml/kg) in ventilated adults with ARDS (Brower et al. 2004).

It is clear that the theoretical benefit of setting PEEP using a deflation limb landmark (Hickling 2001) has yet to be realized in clinical practice. It may be that optimal PEEP on the deflation limb during conventional ventilation is located somewhat below PMC and, when combined with an appropriate tidal volume, can strike the right balance between maintaining lung recruitment and avoiding overdistension. This important physiological question requires further investigation and ultimately will require study in pediatric subjects.

In contrast to the paucity of data in pediatric subject regarding the deflation limb during conventional ventilation, in infants on HFOV the deflation limb has recently been mapped (Fig. 11.21) (Tingay et al. 2006), its landmarks identified, and a strategy for setting mean airway pressure based on identification of closing pressure has been developed (De Jaegere et al. 2006). In this context closing pressure is defined as deterioration in oxygenation with pressure decrements, and setting mean airway pressure 2 cm H₂O higher than this point is associated with stable lung volume and good gas exchange (De Jaegere et al. 2006). This in essence targets a point close to PMC (Tingay et al. 2006) and, given the minimal tidal breath excursions during HFOV, conveys less risk of overdistension than during conventional ventilation. The benefit of mapping the deflation limb during HFOV and the most reliable indicators of optimal airway pressure deserve further scrutiny.

Essentials to Remember

- Static *PV* curves traced at the bedside in ventilated subjects have a recognizable inflation and deflation limb, with landmarks that correlate with lung recruitment, overdistension, and derecruitment.
- There is potential for deflation limb landmarks to guide PEEP setting during conventional ventilation and mean airway pressure setting during HFOV, but in both cases a definitive approach has yet to be formulated, and further research is required.

11.8.2 Pressure–Volume Loops Under Dynamic Conditions

Peter C. Rimensberger, David Tingay, and Peter A. Dargaville

Educational Goals

- To review the differences between a static and a dynamic pressure–volume curve
- To review measurement and calculation methods of dynamic compliance from *PV* loop during ongoing mechanical ventilation
- To review what information can be gathered from *PV* loops displayed on a ventilator screen

11.8.2.1 Measurement of the Dynamic Pressure–Volume Loop

During ongoing mechanical ventilation, a dynamic continuum, dynamic compliance (C_{dyn}) equals the behavior between the pressure difference between P_{plat} and PEEP (ΔP) and tidal volume (V_T) and is expressed as V/P (ml/cm H₂O). The latter has to be reported to the body weight of the patient and will therefore be expressed as ml/cm H₂O/kg.

A prolonged end-inspiratory occlusion (allowing for pressure equilibrium of the respiratory system under zero flow condition) followed by a passive exhalation to ambient pressure at airway opening (zero airway pressure) would allow to measure the static compliance at end-inspiration (i.e., at inspiratory plateau pressure):

$$V_{\text{ei}} / P_{\text{ei}} \text{ above FRC} = C_{\text{statei}}$$

where V_{ei} represents the pressure at end-inspiration, P_{ei} the exhaled volume from end-inspiration to functional residual capacity (FRC), and $C_{\text{stat,ei}}$ the static compliance (i.e., pressure–volume relationship) at end-inspiratory pressure.

Accordingly, an end-expiratory occlusion maneuver followed by a passive exhalation to PEEP will allow to measure the exhaled gas volume to (i.e., tidal volume), giving the compliance

of the respiratory cycle during mechanical ventilation under commonly called “static” conditions

$$C_{\text{stat}} = (P_{\text{ci}} - \text{PEEP}) / V_t = P_{\text{plat}} - \text{PEEP} / V_t$$

This “static” compliance value however reflects a measured value under dynamic conditions (i.e., during ventilation) and can therefore not be compared to the static compliance of the respiratory system that characterizes the *PV-behavior* of the whole respiratory system, from FRC to TLC (Stocks and Jackson 1996) (see Sect. 11.8).

All commonly applied bedside methods of determining C_{rs} and R_{rs} during mechanical ventilation apply mathematical assumptions to model the complex mechanical behavior of the respiratory system.

11.8.2.1.1 Mead Whittenberger Analysis

The Mead and Whittenberger (1953) is an accepted method of calculating C_{rs} during mechanical ventilation. This method determines the C_{rs} and R_{rs} based on an assumption that the respiratory system behaves as a single compartment. This allows the general equation of motion to be applied:

$$P_{\text{TP}} = (E_{\text{rs}} \times V) + (R_{\text{rs}} \times V') + k \quad (11.1)$$

where P_{TP} represents transpulmonary pressure, E_{rs} elastance, V volume, V' flow, and k a constant.

Mead–Whittenberger analysis requires identification of two points of zero flow within the respiratory cycle and assumes these coincide with end-inspiration and end-expiration, when the resistive pressure losses will be zero. Thus, between these two points, the change in P_{TP} will be due to the pressures required to overcome the elastic recoil of the lung (ΔP_{EL}) and

$$\Delta P_{\text{EL}} = E_{\text{rs}} \times \Delta V \quad (11.2)$$

where ΔV represents the change in volume. In dynamic situations this being tidal volume.

This can be reconsidered as

$$C_{\text{rs}} = 1 / E_{\text{rs}} = \Delta V / \Delta P_{\text{TP}}$$

This mathematical determination of C_{rs} requires that the two points of zero pressure correlate with zero flow, limiting use in some circumstances, such as high frequency ventilation (HFV).

11.8.2.1.2 Least-Squares Regression Method

Similar to the Mead–Whittenberger method, the least-squares regression method applies the general equation of motion to a single-compartment model (Davis et al. 1996). Analysis is between two points of the pressure–volume curve. In this case, C_{rs} is determined from the slope of the line joining the maximal and minimal volume during a pressure–volume curve. Again the complex nature of pressure and flow waves, and attenuation, limits this methodology in some ventilatory circumstances.

11.8.2.1.3 Multiple Linear Regression

The multiple linear regression technique uses the entire respiratory cycle to calculate C_{rs} (Stahl et al. 2006). This method is valid during the complex pressure and flow conditions of HFV but requires an analytic process that involves applying an algorithm to minimize errors between the observed pressure changes and the assumed pressure behavior using the equation of motion for the flow and volume measurements. Multiple linear regression is currently impractical outside of a research environment.

Airway resistance is considered to be mainly caused by friction, in phase with flow. The resistive components of the breathing circuit, the endotracheal tube, and the respiratory system cause distortion of dynamic airway pressure measurements during ongoing ventilation.

11.8.2.2 Ventilator Display

Ventilator monitors can and do only display the dynamic *PV* loop, indication on the y-axis the tidal volume delivered and on the x-axis the airway pressures used – therefore, such loops can only describe or visualize the specific dynamic *PV* relationship for a specific airway pressure setting. It must be recognized that mechanical properties of the respiratory system assessed under the dynamic condition of mechanical ventilation are not equivalent to those assessed under static

conditions (Stahl et al. 2006) (see Sect. 11.8.2). There are various reasons for this:

First, during mechanical ventilation or even during spontaneous breathing, the respiratory system never reaches truly static conditions. This is because there is still a continual change in pressure, lowering in exponential fashion over some time, within the system, even when airflow has stopped. To overcome this breathing would have to be interrupted for several seconds. Since this is hardly possible in the clinical setting without muscle paralysis, the *PV* loop that can be displayed on a ventilator remains a dynamic measure even when a zero flow condition is reached at end-inspiration and end-expiration, and its shape will depend on airway resistance (i.e., equipment and patient airway resistance). This latter effect could be only overcome by very low-flow conditions that again are not practical in a non-paralyzed patient. *PV* hysteresis seen on the dynamic *PV* loop is therefore mainly due to airway resistance, and the effect of airway resistance is most marked during high flows, i.e., at the beginning of inspiration and at the beginning of expiration, respectively. This results in the appearance of a change in the curvature of the inflation limb at the lower volume end on the volume axis (often referred to as the “lower inflection point”) and similarly in a change of the curvature of the deflation limb at the upper end on the volume axis (often referred to as the “upper deflection point”) (see Fig. 11.27). However, such phenomena are a result of initial fast flows during inflation and deflation in a highly resistive system (endotracheal tube) during a rapid increase or decrease of pressure gradient between applied airway pressures at airway opening (i.e., close to or at the endotracheal tube connection) and effective airway pressure at the alveolar level. Since by the ventilator displayed airway pressures are measured at the endotracheal tube connector (i.e., before the part of high resistance in the respiratory circuit that includes the endotracheal tube) and not on the tracheal level (Karason et al. 2000) (Fig. 11.27), this dynamic *PV* loop cannot give an indication on the level of pressures required (i.e., PEEP) for understanding when the lungs start to open and to set PEEP accordingly, as has been

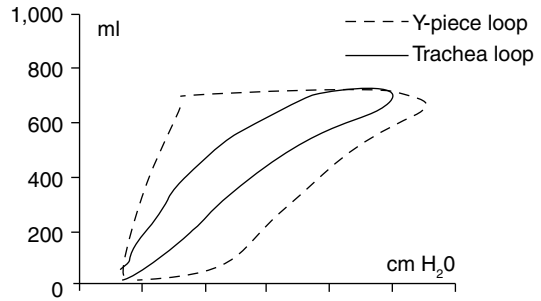


Fig. 11.27 Pressure–volume (*PV*) loop during mechanical ventilation with an extrinsic PEEP of 8 cm H₂O. The *dashed line* shows the dynamic *PV* loop with pressure measurement at the airway opening (i.e., at endotracheal tube connector), the *solid line* shows the dynamic *PV* loop derived from a pressure measurement at the endotracheal tube tip, i.e., carinal level. Note the difference in the amount of *PV* hysteresis and the appearance of a lower inflection point (LIP) on the inflation limb of the *PV* loop derived from pressure measurements at airway opening. This LIP cannot be identified on the *PV* loop derived from pressure measurements at the carina level. Similarly, there is appearance of a deflection point on the deflation limb and the appearance of the *PV* loop derived from pressure measurements at airway opening. Again, this deflection point cannot be identified on the *PV* loop derived from pressure measurements at the carina level. However, on the inflation limb there is appearance of an upper inflection point with a flattening of the *PV* curve at the upper end (lower compliance at the higher-pressure end, which may indicate overinflation of the lungs. (see also Fig. 11.5). However, this is not a very marked point but rather a successive phenomenon (With permission from Karason et al. (2000))

suggested in various textbooks and guidelines on how to optimize mechanical ventilation.

Second, although the recruiting effect of PIP pushes the high-pressure end of the dynamic *PV* loop during ongoing ventilation onto the inflation limb of the static *PV* curve, the end-expiratory volume is found, during ongoing ventilation at any PEEP level (with the exception of a zero PEEP condition), to be above the corresponding *PV*-value on the inflation limb of the semi-static or static *PV* curve (Fig. 11.28) (Stahl et al. 2006; Rimensberger et al. 1999). In contrast, during decremental PEEP steps after recruitment to TLC, dynamic compliance (i.e., the deflation part of the dynamic *PV* loop) will be in close agreement with the deflation limb of the *PV* curve, the end-expiratory volume at PEEP (as long as lung collapse does not occur) being placed on the deflation limb of the static *PV* curve (Figs. 11.29 and 11.30).

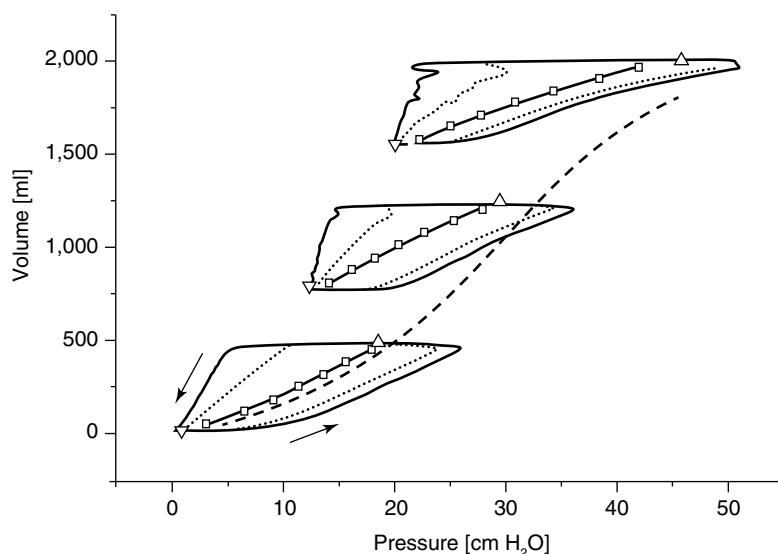


Fig. 11.28 Dynamic and static pressure–volume (PV) curves and compliance values of a patient. Note that the inflation limb of the dynamic alveolar PV (dotted line) at zero end-expiratory pressure and the static PV curve, resulting from low-flow inflation (dashed line) are in close agreement, whereas the dynamic alveolar PV curves at positive end-expiratory pressure (PEEP) of 12 cm H₂O and PEEP of 20 cm H₂O are not in agreement with the static PV curve. Dynamic compliance (square line) during

mechanical ventilation differs for any setting clearly from the static compliance (dashed line) inflation curve to maximal inspiratory capacity of the respiratory system. Lower and upper inflection points (LIP and UIP, respectively) derived from the static PV curve do not correspond to the effect of PEEP on lung volumes. Arrows indicate the inflation and deflation part of the dynamic PV-curves (solid line) as displayed on the ventilator screen. (Reprinted with permission from Stahl et al. (2006))

This is the result of a different behavior of the lung during inflation and deflation (i.e., hysteresis) (Rahn et al. 1946) (see also Fig. 11.25).

The observations that (1) the inflation limb of the quasistatic PV curve (as generated by the super-syringe or low-flow inflation methods) is distinctly different from the deflation limb, (2) the inflation limb is highly sensitive to the initial inflation conditions (i.e., whether inflation starts from zero PEEP or another PEEP level) (Jonson et al. 1999) and preceding lung history (i.e., whether the patient was disconnected or even suctioned shortly before), and (3) the tidal cycle is not placed on the inflation limb of the quasistatic PV curve (Figs. 11.28, 11.29, and 11.30) (Stahl et al. 2006; Rimensberger et al. 1999) clearly illustrate how difficult it can be to use the slope of the tidal cycle PV curve (i.e., dynamic compliance) during incremental stepwise titration of PEEP as the only indicator for the best ventilator settings, as historically suggested (Suter et al. 1975, 1978).

Essentials to Remember

- The static and dynamic PV loops do not provide the same information and are not interchangeable in guiding the best ventilator settings.
- The slope of the PV loop (i.e., dynamic compliance) might be helpful to assess respiratory system behavior in a dynamic way, during incremental and decremental PEEP steps, but not when assessed at one single ventilator setting when lung history cannot be taken in account.
- The PV slope displayed on the ventilator is based on pressure measurements at the airway opening (i.e., endotracheal tube connector) and mainly reflects airway and endotracheal tube resistance. Therefore, it cannot give an indication on the level of pressures required (i.e., PEEP) to optimally support the lung during mechanical ventilation.

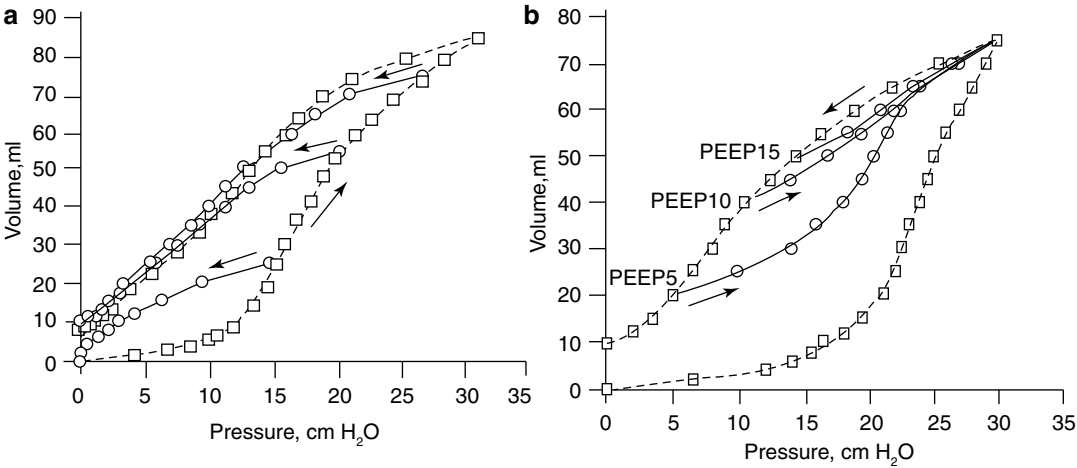


Fig. 11.29 Simulation of positive pressure ventilation using an air-filled syringe. (a) Pressure/volume envelope of the surfactant-depleted washed lung (dashed line) with deflation curves (solid lines) from three different pressure levels (15, 20, and 25 cm H₂O), corresponding to positive inspiratory pressure (PIP), to functional residual capacity. (b) Pressure/volume envelope of the saline-lavaged lung

(dashed line) with reinflation to 30 cm H₂O (solid lines) after deflation to three different pressure levels (5, 10, and 15 cm H₂O) corresponding to positive end-expiratory pressure (PEEP). Arrows indicate whether the pressure was stepwise increased or decreased when creating this part of the curve. (Reprinted with permission from Rimensberger et al. (1999))

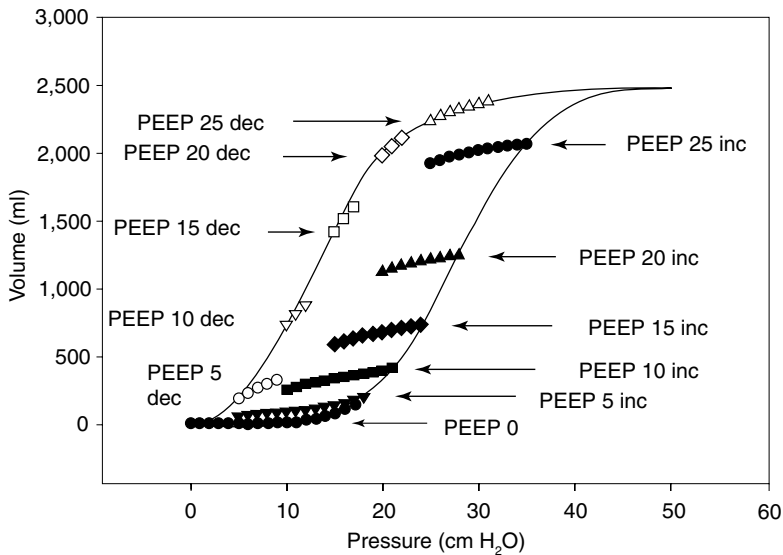


Fig. 11.30 Inspiratory tidal PV plots with V_T 140 ml with incremental (black symbols) and decremental (open symbols) PEEP levels from 0 to 25 cm H₂O derived mathematically from a multiple units lung model. At each PEEP level the volume at equivalent pressures and the mean tidal PV slope (i.e., tidal cycle compliance or dynamic

compliance during conventional mechanical ventilation) are greater during decremental PEEP. With zero PEEP, the plots for incremental and decremental PEEP are superimposed. Note that the dynamic tidal PV cycle is never positioned on the plotted inflation limb of the overall PV curve (Reprinted with permission from Hickling (2001))

11.9 Respiratory Mechanics in the Actively Breathing Patient with/Without Respiratory Support

Mark Heulitt and Sherry Courtney

Educational Aims

- To understand the physiologic basis of the measurement of work of breathing
- To understand the subdivisions of WOB attributed to the patient (WOB_p , physiologic) and those associated with the ventilator (WOB_v , imposed) and how these measures can be used by the clinician as predictors of weaning or to perform accurate measurement of elastic, flow-resistive, and imposed work during mechanical ventilation to guide the level of support or to guide specific selection of the ventilator mode
- To understand the limitations of measurement of WOB to the clinician in weaning ventilatory support or selection of ventilatory mode

11.9.1 Introduction

Work of breathing (WOB) is a common term used to describe respiratory work in both patients who are breathing spontaneously and those requiring the support of mechanical ventilation. It represents an assessment of the afterload on the respiratory muscles or opposition to their contraction. During mechanical ventilation the goal is to assist respiratory muscle activity and thus reduce the WOB but not to entirely eliminate it. During spontaneous breathing there is active contraction of the respiratory muscles resulting in expansion of the thoracic compartment with a subsequent decrease in pleural pressure. Lung expansion results from the negative pressure generated and air flows into the lung due to the decrease in alveolar pressure below atmospheric pressure. Work of breathing can be subdivided into the work necessary to overcome the resistive, elastic,

and inertial components and the work required to move the chest wall and intestinal organs. To understand the impact of mechanical ventilation on WOB, it is necessary to understand the forces that respiratory muscles must work against to allow for gas exchange to occur. These forces are the components that must be measured to accurately determine WOB. The reader is encouraged to read the excellent review by Banner (1994) for further discussion of this topic. A summary of some important concepts from this review is presented in the (Table 11.1). Our discussion will focus on the physiologic principals of WOB measurement and its clinical relevance for the care of mechanically ventilated infants and children.

11.9.2 Concept and Methods of Measurements

Work is equal to the product of the force applied to an object and the distance the object travels; that is, work = force $\times$ distance, or $W = F \times D$.

However, if we describe work in the three dimensions that apply to the respiratory system, work becomes the pressure applied to yield a change in volume of the system and can be expressed as

$$W = P \times V$$

or

$$W = \int_0^V P \times dv$$

where $\int_0^V P$ is the integral of the pressure across the respiratory system as a function of volume and dv is the change in the volume of the respiratory system. When respiratory muscles contract, displacement occurs and mechanical work occurs. The muscles act as force generators, but the diaphragm generates 70 % of the tidal volume exchanged. The diaphragm is composed of three types of classic muscle fibers that differ in their ability to resist fatigue or lose the force-generating capacity of the muscle. Type 1 muscle fibers or slow oxidative fibers compose approximately 60 % of the diaphragm in adults and are very resistant to fatigue, allowing them to

Table 11.1 Influence of the site of pressure measurement and mode of ventilation on measurement of work of breathing and compliance

Site of pressure measurement and mode of ventilation	Area of the pressure–volume loop = work done to overcome	Slope of the pressure–volume loop
Esophageal pressure during mechanical spontaneous ventilation	Pulmonary inspiratory and expiratory resistance	Lung compliance
Esophageal pressure during mechanical ventilation	Chest wall inspiratory and expiratory resistance	Chest wall compliance
Pressure at tracheal (carinal) end of endotracheal tube during spontaneous breathing	Imposed inspiratory and expiratory resistance of the total breathing apparatus (i.e., ET, breathing circuit, and the ventilator)	Compliance of the total breathing apparatus
Pressure at tracheal (carinal) end of endotracheal tube during mechanical ventilation	Pulmonary and chest wall inspiratory and expiratory resistance	Compliances of the respiratory system (lung plus chest wall)
Pressure at the airway opening (between the Y-piece of breathing circuit and endotracheal tube) during spontaneous ventilation	Imposed inspiratory and expiratory resistance of the breathing circuit and ventilator	Compliance of the breathing circuitry
Pressure at the airway opening during mechanical ventilation	Pulmonary and chest wall inspiratory and expiratory resistance, plus resistance of the endotracheal tube	Compliance of the respiratory system (lung plus chest wall)

From Banner (1994)

maintain contractility for longer periods but generating less force than other muscle fibers (Braun et al. 1983).

Muscle contractions can be characterized depending upon where this work is performed. During miometric contractions, the muscle shortens and the performed work is called positive (i.e., the muscle performs work on something). During plyometric contraction, the muscle lengthens as the result of a larger, oppositely applied force and the work performed is negative (i.e., something does work on the muscle). During isometric contraction no displacement takes place and therefore no mechanical work is performed; however, there is a metabolic cost for the respiratory muscles performing this contraction. The type of contraction may have a direct impact on the patient's outcome on mechanical ventilation. For example, it has been hypothesized that plyometric contractions may be associated with respiratory muscle damage and inability for patients to tolerate weaning from mechanical ventilatory support. The ultimate result of any respiratory muscle contraction is to perform the necessary work needed to overcome opposing forces in the respiratory system. These forces are usually

characterized as representing either the elastic or flow-resistive components of the respiratory system. However, in reality the forces are more complex, representing (1) the stress adaption within the lungs and chest wall (e.g., viscoelastic) within thoracic tissues, (2) the differences in static and elastic recoil of the lung and chest wall during inflation and deflation (e.g., plastoelastic), (3) the mass of tissues and gases (inertial and gravitational), (4) compression and distension of intrathoracic gas, and (5) forces that distort the chest wall from its relaxed configuration (distorting forces are small at rest but may contribute). However, during mechanical ventilation these forces are small; thus, traditionally only elastic and flow-resistive forces are accounted for in the calculation of WOB.

Most important is the ability of the respiratory muscles to tolerate increasing load; otherwise, the ultimate fatigue will lead to the need for mechanical ventilatory support. Increasing muscle loading leads to an imbalance between respiratory muscle energy supply and demand due to the need for increased muscle blood flow and oxygen consumption. This imbalance can lead to muscle ischemia, fatigue, and respiratory failure due

to an energy deficit and the inability to remove metabolites from the muscles (Bellemare et al. 1983). Increased muscle loading has a predictable sequence leading to muscle fatigue. Increased muscle loading leads to an increased force of contraction of respiratory muscles, which can be measured by measuring the transdiaphragmatic pressure (P_{di}), and increased duration of contraction of the respiratory muscles can be illustrated by a change in the ratio of the inspiratory time to total cycle time (T_I/T_{tot}). Subsequently these changes lead to an increased tension–time index of the major respiratory muscle, the diaphragm ($P_{di}/P_{dimax} \times T_I/T_{tot}$), and increased muscle energy demands with a need for increased blood flow, oxygen, and nutrients. The ultimate result of this sequence is respiratory muscle fatigue that represents an imbalance between demand (work of breathing and afterload) and supply (blood flow, oxygen, and nutrients).

Clinical manifestations of respiratory muscle fatigue also follow a predictable sequence that has been utilized for predicting patient fatigue and ability to wean from mechanical ventilator support. The clinical manifestations of respiratory muscle fatigue sequence include increased respiratory rate, development of discoordinate respiratory movements (i.e., abdominal paradox and respiratory alternans), increase in $PaCO_2$, respiratory acidemia, and terminal decrease in respiratory rate and minute ventilation. Measures of WOB have been proposed as a way the clinician can balance the factors associated with respiratory muscle fatigue, thus allowing patients to breath spontaneously during mechanical ventilator support, given that the goal of this support in respiratory failure is to decrease afterload (WOB) on the respiratory muscles.

11.9.3 Measurements of the Energetics of Breathing

11.9.3.1 Work of Breathing

In the pressure–volume curve for the calculation of WOB, the pressure needs to represent changes in intrathoracic pressure, more specifically, pleural pressure.

Thus, mechanical WOB can be calculated by measuring the generation of intrathoracic pressure due to contraction of the respiratory muscles (P_{mus}) and/or the applied pressure from the ventilator (P_{appl}). The total pressure generated at the airway (P_{aw}) is thus the sum of P_{mus} and P_{appl} . These pressure changes are related to the generated pressure differences needed to overcome forces from different components of the respiratory system such as the lung, chest wall, and respiratory system. These pressure differences are related to ventilation and thus movement of gas. Below are the calculations necessary to express these pressure differences, depending upon forces to be overcome.

For the pressure differences across the lung, called transpulmonary pressure (P_L),

$P_L = P_{aw} - P_{pl}$ where P_{aw} is airway pressure and P_{pl} is pleural pressure.

For the pressure differences across the chest wall (P_{CW}),

$P_{CW} = P_{pl} - P_{bs}$ where P_{pl} is pleural pressure and P_{bs} is body surface pressure.

For the pressure differences across the respiratory system (P_{RS}),

$$P_{RS} = P_{aw} - P_{bs}$$

Alternatively,

$$\begin{aligned} P_{RS} &= P_L + P_{CW} \\ &= P_{aw} - P_{pl} + P_{pl} - P_{bs} \\ &= P_{aw} - P_{bs} \end{aligned}$$

The pressure differences above are important because the lung and chest wall move together, conjoined by a potential space formed by the two pleural linings. The pressure in the pleural space is denoted P_{pl} , and at rest in the upright human, it is slightly negative, because the lung is a passive structure that is elastic and has a tendency to recoil to a smaller volume than the respiratory system combination (lung and chest wall together). The lung is prevented from collapsing because of the tendency of the chest wall to recoil outwards and the negative value of P_{pl} . At the end of a relaxed exhalation (to functional residual capacity) and with the mouth open, the alveolar pressure (P_{alv}), the pressure of the airway opening (P_{AO}), and the

atmospheric pressure (P_{atm}) are equal. Thus, at functional residual capacity with the mouth open, the distending pressure of the lung (P_L) is equal to the pressure inside the lung P_{alv} (which in this case is equal to P_{atm}) minus the pressure in the pleural space. The importance of this is that the distending pressure across the lung (transpulmonary) determines the lung volume. Therefore, the changes in distending pressure result in changes in lung volume and thus ventilation. In order to understand ventilation, we must understand and be able to measure P_{pl} and P_{alv} . This will in turn allow us to calculate the distending pressure of the lung, chest wall, and respiratory system.

P_{alv} is measured by assessing P_{AO} during static maneuvers when, with an open glottis and uninterrupted airway, $P_{\text{alv}} = P_{\text{AO}} = P_{\text{atm}}$. We can easily measure P_{atm} and by convention P_{atm} is said to equal a pressure of zero. P_{pl} is measurable directly only by placing a catheter in the pleural space, which is not usually possible in clinical practice. Fortunately, the pressure in the lower third of the esophagus (P_{es}) closely approximates the pressure in the adjacent pleura when the subject is in the upright posture, due to the close proximity of the esophagus to the pleural space. Because the body of the esophagus is essentially a passive structure (except during a swallow), able to transmit pressure from the adjacent pleural space (P_{pl}) to a measurement catheter in the esophagus, P_{es} is a reasonably close surrogate for P_{pl} in a human being in the upright posture. This does not necessarily hold true in the supine position, in which the mediastinum may compress the esophagus. Compression of the posterior and inferior portions of the lung can create large regional differences in pleural pressure.

In addition to the measurement of P_{es} , it is also possible to measure gastric pressure (P_{ga}) by placing another catheter more distally, in the stomach. P_{ga} closely approximates the pressure in the abdominal cavity. With accurate measurements of P_{pl} and abdominal cavity pressure, a wide variety of useful measurements of the mechanical respiratory system can be made.

During normal, unassisted, spontaneous inhalation, pressure is generated by the respiratory muscles (P_{mus}) to overcome the elastic and

resistive pressures of the respiratory system. Elastic pressure (P_{el}) is the product of respiratory system elastance (E_{st}) (reciprocal of compliance) and volume (V) such that

$$P_{\text{el}} = E_{\text{st}} (\text{cm H}_2\text{O} / \text{L}) \times V (\text{L})$$

Resistive pressure (P_{res}) is the product of total resistance (respiratory system plus breathing apparatus resistance, R_{TOT}) and inspiratory flow rate ($\dot{V}$ (L/s)), that is,

$$P_{\text{res}} = R_{\text{TOT}} (\text{cm H}_2\text{O} / \text{L} / \text{s}) \times (\text{L} / \text{s})$$

Under normal conditions in adults, the change in the pressure generated by the respiratory muscles is approximately 5 cm H₂O. When there is increased elastance and/or resistance, the respiratory muscles are loaded and thus work of breathing increases:

$$P_{\text{mus}} = P_{\text{el}} + P_{\text{res}}$$

This increase in respiratory muscle pressure can be decreased when the respiratory muscles are unloaded with an appropriate level of ventilator support (e.g., PSV):

$$P_{\text{mus}} = (P_{\text{el}} + P_{\text{res}}) - \text{PSV}$$

Thus, the ventilator becomes an extension of the patient's respiratory muscles, causing partial unloading of the respiratory muscles and sharing of the load between the respiratory muscles and the ventilator.

These interactions during mechanical ventilation can be summarized by Newton's equation of motion, with presence of intrinsic PEEP adding to respiratory loading by increasing expiratory airway resistance and/or by inadequate exhalation time:

$$P_{\text{mus}} + P_{\text{appl}} = \text{PEEP}_i (\text{intrinsic PEEP}) + P_{\text{res}} + P_{\text{el}}$$

Thus, factors affecting the load of respiratory muscles can be subdivided into physiologic factors and factors associated with the breathing apparatus. The physiologic factors include elastic work (lung and chest wall compliance),

resistive work (apparatus), inspiratory flow rate demand, alveolar minute ventilation, and dead space. Breathing apparatus factors include the imposed work associated with the endotracheal tube and ventilator, sensitivity and trigger setting, response time of the ventilator, and method of triggering the ventilator. For factors associated with the breathing apparatus, the endotracheal tube is probably the most important resistor associated with increased WOB, secondary to the increased resistive workload. This effect is most exaggerated in neonatal and pediatric patients who have smaller endotracheal tubes (Lesouf et al. 1984).

WOB can be calculated utilizing the Campbell diagram in Fig. 11.31 (Campbell 1958), which illustrates the dynamic relationship between pleural pressure and lung volume. Since pleural pressure is difficult to measure, the surrogate measurement of esophageal pressure is commonly utilized for both research and clinical applications of WOB measurement. Esophageal pressure swings during inspiration need to overcome two forces: the elastic forces of the lung parenchyma and chest wall and the resistive forces generated by the movement of gas through the airways. One can calculate these two components (elastic and resistive) by comparing the difference between esophageal pressure during the patient's effort (the breath) and the pressure value under passive conditions, represented by the static volume–pressure curve of the relaxed chest wall. This passive volume–pressure curve is a crucial component of the Campbell diagram (Fig. 11.31). It is calculated from the values of esophageal pressure and lung volume obtained when the airways are closed and the muscles are completely relaxed. The volume of functional residual capacity results from the expansion of the lung and reduction in chest wall volume. During spontaneous inhalation, intrapleural pressure decreases and volume increases. The elastic work required to expand the lungs is defined in the diagram as the triangular-shaped area subtended by the lung and chest wall compliance curves. This elastic work done by the respiratory muscle is less than that illustrated by the diagram because

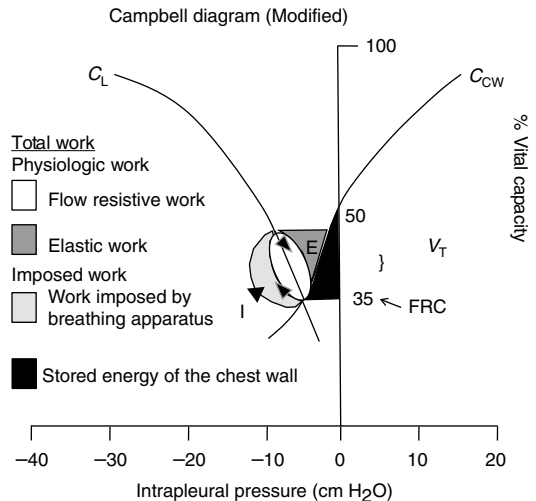


Fig. 11.31 Representation of the total work of breathing using a modified version of the Campbell diagram. Compliance curves of the lungs (C_L) and chest wall (C_{CW}) are shown in relationship to volume and intrapleural pressure and intersect at functional residual capacity (FRC). During spontaneous inhalation (I), tidal volume (V_T) increases, while intrapleural pressure decreases (upward pointing arrow of inner pressure–volume loop). Exhalation (E) is normally passive. The inspiratory portion of the loop (vertical lines) is the physiologic inspiratory flow-resistive work of breathing. The physiologic elastic work of breathing is the triangular-shaped area subtended by the compliance curves (diagonal lines). The Campbell diagram is modified to include the additional flow-resistive workload (outer pressure–volume loop) imposed by the breathing apparatus (endotracheal tube, breathing circuit, and ventilator, stippled area). The total work of breathing for a spontaneously breathing, intubated patient attached to a ventilator is the physiologic plus the imposed work of breathing (From Banner (1994))

of energy stored and recovered from chest wall displacement. The elasticity of the chest wall (tendency to recoil outward) is actually assisting the inflation of the lungs; conversely, it opposes exhalation. Unfortunately, as this is difficult to measure (because it requires passive inflation and often muscle paralysis), a theoretical value for the slope of this curve is frequently used in lieu of the exact measurement. However, if the patient does not require neuromuscular blockade with muscle relaxant, a true value for the volume–pressure relationship of the chest wall can be obtained during passive tidal breathing (Jubran et al. 1995). Thus, for subsequent breaths when the patient develops spontaneous

calculating values of work performed on the lung. During spontaneous breathing, P_{aw} is zero, and thus, inspiratory work can be calculated from the P_{es} and volume recordings alone. In a patient connected to ventilator circuit, P_{aw} is not zero, with the result that measurement of P_{es} alone does not permit calculation of work performed by the patient. Work performed by the ventilator or work imposed on the patient by the ventilator and external circuit still requires measurements of P_{aw} and volume. Measurements of total work during spontaneous efforts while a patient is attached to a ventilator require measurement of both P_{es} and P_{aw} (as well as volume).

It is essential, in order to clinically apply measurements of WOB, to differentiate not only differentiate the patient and ventilator components but also those associated with the work necessary to overcome the resistive and elastic components. Theoretically elastic changes reflect the patient's disease state and the reason the patient required mechanical ventilatory support as well as the opposing forces that create work. Those opposing forces can be subdivided into mechanical, or volumetric, and ventilator induced, or isometric. Mechanical opposing forces consist of the elastic aspects of the compliance of the lung and chest wall and the frictional forces of airway resistance. In contrast ventilator-opposing forces consist of effects of the ventilator demand system and circuit and presence of intrinsic PEEP.

Thus,

$$WOB_p = WOB_{pl} + WOB_{pcw}$$

Work on the lung is calculated in the traditional way:

$$WOB_{pl} = (P_{ee} - P_{es}) \times \frac{dV}{dt},$$

where P_{ee} is end-expiratory esophageal pressure.

Work on the chest wall for spontaneously breathing patient is calculated from tidal volume and chest wall compliance according to the following formula:

$$WOB_{pcw} = \frac{1}{2} \times V_T^2 \times C_{cw}$$

During patient-triggered ventilator-assisted breaths, a portion of the tidal volume is delivered due to patient's effort, as indicated by negative delta P_{es} , and the other portion is delivered by the ventilator, as indicated by a P_{aw} that is greater than P_{atm} . The portion of tidal volume inspired solely due to patient's effort is designated V_p . Thus, for mechanically ventilated patients, patient volume must be used instead of tidal volume:

$$WOB_{pcw} = \frac{1}{2} \times V_p^2 \times C_{cw}$$

$$V_T = V_p + V_v$$

For this equation the ratio of V_p to V_v is the same as the ratio of corresponding driving pressures. Since the ratio of delta P_{es} and delta P_{aw} varies through inspiration, the proportion must be determined from continuous integration of these pressures per the following formula:

$$V_p = \frac{(P_{ee} - P_{es})}{[(P_{aw} - P_{atm}) + (P_{ee} - P_{es})]} dV/dt$$

If there is no patient effort, then $(P_{ee} - P_{es}) = 0$ and $V_p = 0$. If $P_{aw} = P_{atm}$ then $V_p = V_T$. To calculate WOB the integration limits must be determined from the start until the end of inspiration. The end of inspiration occurs when P_{es} becomes greater than P_{ee} .

P_{ee} : end-expiratory esophageal pressure

P_{es} : esophageal pressure

P_{aw} : airway pressure

P_{atm} : atmospheric pressure

V_p : patient volume

V_v : ventilator volume

V_T : tidal volume

C_{cw} : chest wall compliance (if not measured is assumed to be 200 ml/cm H₂O)

dV/dt : instantaneous flow

11.9.3.2 Flow-Resistive Work

Total resistive work done on the lungs during assisted breathing is obtained by integrating the area subtended by P_{es} and lung volume during a single breath. Work is partitioned into its inspiratory and expiratory resistive components by drawing a line between the points of zero

flow: the dynamic pulmonary compliance line. In Fig. 11.31 the area enclosed by the ellipse to the left of the line represents inspiratory resistive work, while the area to the right of this line represents expiratory resistive work. If the expiratory portion of the loop falls within the area representing elastic work, expiratory resistive work will be performed passively at the expense of the elastic energy stored in tissues deformed during inspiration. Measurement of resistive work using P_{es} includes work performed in overcoming the flow resistance of equipment in addition to the flow resistance of the lung.

Figure 11.32 (Campbell loop with increased resistance) illustrates increased resistance with subsequent increased flow-resistive work of breathing. Increased resistance can be due to increased resistance in the airways (i.e., bronchial obstruction or constriction) or changes in the breathing apparatus (i.e., secretions in endotracheal tube). In this example both inspiratory and expiratory muscles are loaded and active. Increased work of breathing is depicted as increased area in the inspiration and expiration parts of the pressure–volume loop.

11.9.3.3 Elastic Work

During unassisted breathing, work performed by the inspiratory muscles against elastic recoil of the lungs and chest wall can be calculated using volume versus esophageal pressure, utilizing measurement of the static compliance of the chest wall (C_{CW}). This can be estimated by recording P_{es} and volume during controlled ventilation while respiratory muscles are completely relaxed. Pressure developed by the respiratory muscles in expanding the chest wall is obtained from subtraction of P_{es} from P_{CW} .

In examining the pressure–volume loop for the calculation of C_{CW} during mechanical ventilation, inactivity of the respiratory muscles is determined by noting the formation of a P_{es} –volume loop in a counterclockwise direction. The loop is reasonably narrow, and the axis of the loop is rotated farther to the right as the level of ventilatory support is increased. On occasion, a neuromuscular blocking agent may be needed to achieve adequate respiratory muscle relaxation.

Decreased lung compliance

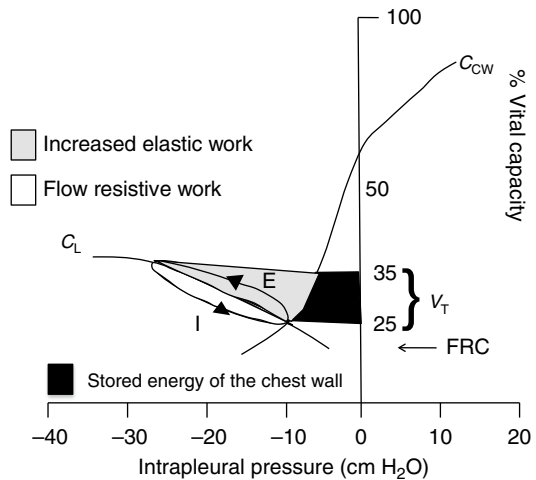


Fig. 11.33 Decreased lung compliance (C_L) results in increased elastic work of breathing. Total work of breathing includes flow-resistive work on the airways and tissues and increased elastic work done on the lungs by the respiratory muscles during spontaneous inflation of tidal volume (V_T), starting from a decreased functional residual capacity (FRC). C_{CW} chest wall compliance, I inhalation, E exhalation (From Banner (1994))

In Fig. 11.33, we illustrate an increase in elastic work resulting from a decrease in lung and/or chest wall compliance. Lung compliance changes are consistent with pulmonary disease that alters pulmonary compliance (i.e., ARDS, pneumonia), and chest wall compliance changes can be seen in diseases that affect the chest wall directly (i.e., kyphoscoliosis) or indirectly (i.e., abdominal distension).

Decreased compliance inversely affects elastic work of breathing for either the lung or chest wall. Decreased chest wall compliance is illustrated in Fig. 11.34. Subsequently as compliance decreases, there is direct correlation to changes in tidal volume. Patients compensate with either increased respiratory effort or attempts to improve functional residual capacity.

11.9.3.4 Expiratory Work

Expiration is passive with work being performed entirely during inspiration. Total work performed is distributed evenly between work dissipated as heat in overcoming flow-resistive work and the work which is stored as potential energy in the deformed

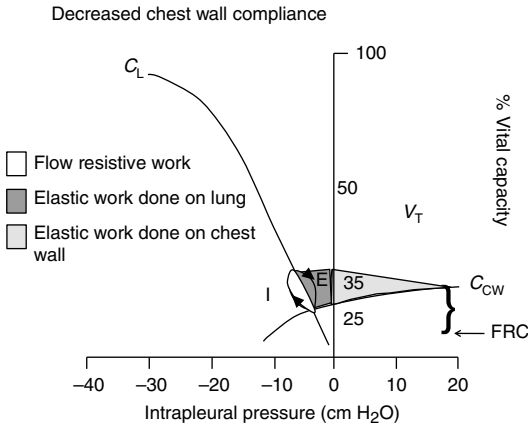


Fig. 11.34 Decreased chest wall compliance (C_{CW}) results in increased elastic work of breathing. Total work of breathing includes flow-resistive work on the airways and tissues, elastic work done by the lungs, and elastic work done on the chest wall by the respiratory muscles during spontaneous inflation of tidal volume (V_T), starting from decreased functional residual capacity (FRC). C_{CW} chest wall compliance, I inhalation, E exhalation (From Banner (1994))

tissues of the lungs and chest wall for use during expiration. Normally this stored work is transferred to inspiratory muscles except when there is markedly increased expiratory resistance resulting in recruitment of expiratory muscles. Use of expiratory muscles increases P_{es} , producing P_{es} -volume values to the right of the chest wall relaxation line and outside the elastic work of the Campbell diagram. In this situation, P_{es} is higher than the elastic recoil pressure of the chest wall. Expiratory work can be quantified as the area enclosed by the expiratory portion of the P_{es} -volume loop to the right of the chest wall relaxation line. This measurement can underestimate expiratory work in proportion to the amount of work needed to overcome the expiratory resistance of the chest wall.

11.9.3.5 Negative Inspiratory Work

Some of the energy stored in the tissues during inspiration is used during the expiratory phase of the respiratory cycle to overcome flow resistances of the lung and chest wall, with the remainder being used to overcome the persistent activity of the inspiratory muscles during expiration. Since this post-inspiratory work performed is considered negative (i.e., something does work on the muscle), it is classified as plyometric.

This negative work is substantial during normal resting ventilation but becomes small with increasing ventilation. It can be calculated by subtracting expiratory-flow-resistive work from the elastic work of inspiration. Overall, the energy cost of negative work performed by the inspiratory muscles during expiration is considered negligible.

11.9.3.6 Work Units

For work the most popular units are kilograms·meters ($\text{kg}\cdot\text{m}$) and joules (J). One joule is the energy needed to accelerate a 1 kg mass 1 m/s/s. Because the force of gravity accelerates objects at 9.8 m/s^2 , thus,

1 $\text{kg}\cdot\text{m}$ (a force equal to the weight of 1 kg applied over 1 m) is equivalent to 9.8 J

1 J = energy needed to raise 1 kg 10.2 cm against the force of gravity

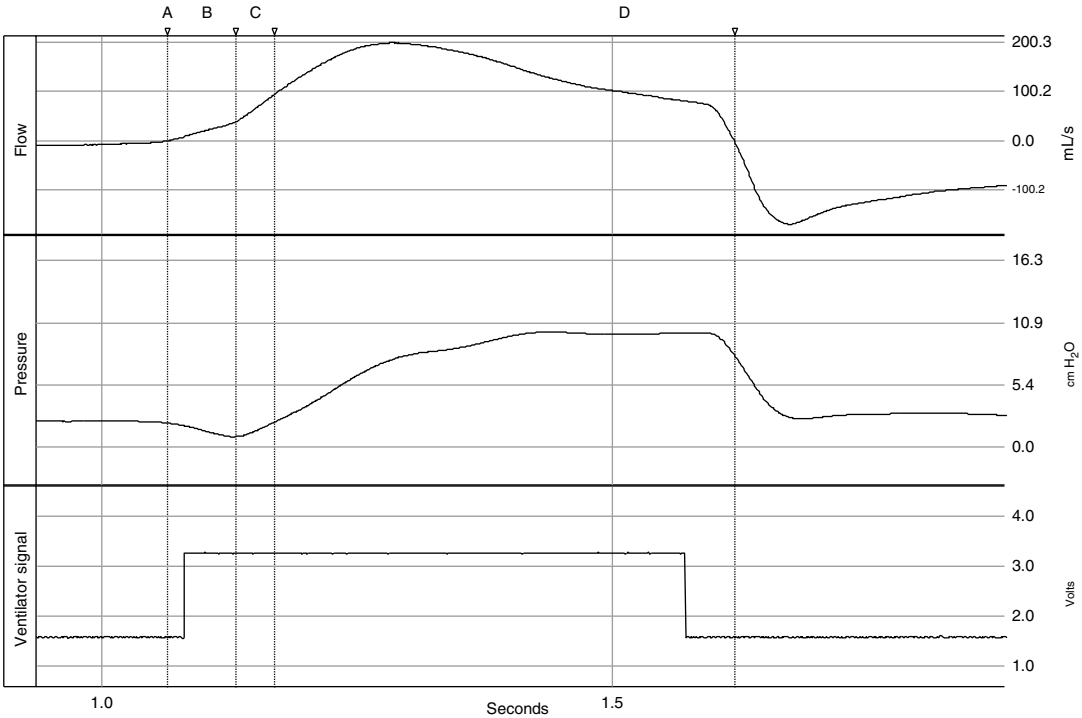
$$1 \text{ W} = 1 \text{ J/s}$$

$$1 \text{ cal} = 4.184 \text{ J}$$

In general, $0.1 \text{ kg}\cdot\text{m}$ approximates 1 J, and this can be thought of as the energy that is needed to move 1 l through a 10 cm H_2O pressure gradient.

11.9.3.7 Pressure-Time Product

In the case of ineffective respiratory effort, that is, muscle contraction without volume displacement, WOB cannot be measured from the Campbell diagram, since the calculation is based on volume displacement. A measure that appears to more closely approximate oxygen cost of breathing or energy expenditure of the muscles is the pressure-time product (P_{TP}). The P_{TP} is the product of the pressure developed by the respiratory muscles multiplied by the time of muscle contraction, expressed in cm H_2O per second, and described in Fig. 11.35. The relevant pressure is again the difference between the measured esophageal pressure and the static relaxation curve of the chest wall. The pressure measurement most often used in this calculation is P_{es} . For patients receiving volume-controlled ventilation where tidal volume is predetermined, the calculation is straightforward. Unfortunately, in a mode of ventilation where inspiratory flow can vary breath to breath, this calculation can be



A—initiation of breath (zero flow)
 B—beginning of ventilator pressurization
 C—return to baseline pressure
 D—end inspiration

A–B = Trigger Delay and PTP Area A
 B–C = Response Time and PTP Area B
 A–C = PTP Area 1 (Area A and Area B)
 C–D = PTP Area 2 (PTP of pressure curve during inspiration)

Fig. 11.35 The pressurization of the respiratory system can be subdivided into the inspiratory positive pressure area or P_{TP} area 2, C–D (Chatmongkolchart et al. 2001), which follows P_{TP} area 1, A–C, and is the amount of effort expended to activate the mechanical breath. Area 2 is defined by the start of the inspiratory pressure curve with the return of pressure to baseline and ending at the onset

of expiration. Area 2 represents the ability of the ventilator to pressurize the system or the actual area of pressure versus time applied during inspiration. The figure represents the time in ms from the point where the breath is initiated (where flow crosses the zero line) till point of peak inspiratory pressure. This represents the sum of the subject's effort and the response time of the ventilator

difficult. However, it can be calculated utilizing the upper and lower bounds of the pressure–time product for patients in pressure support ventilation (Jubran and Tobin 1997). P_{TP} varies directly with total lung resistance.

P_{TP} is measured as the integral of esophageal pressure and time for the duration of contraction of the respiratory muscle.

Thus,

$$P_{TP} = \left[(P_{EE} - P_{ES}) + (Vol / C_{CW}) \right] dt / t_{min} \quad \text{while } P_{ES} \text{ is greater than } P_{EE}$$

P_{EE} = end esophageal pressure

P_{ES} = current esophageal pressure

Vol = current tidal volume

C_{CW} = chest wall compliance (assumed at 200 ml/cm H₂O)

dt = sample time

t_{min} = duration of breath in minutes

Another measure is pressure–time index (PTI), which is a measure of strength and endurance combined into one value. It combines the strength measurements of P_{ES} and maximum inspiratory pressure during occlusion with the endurance value of the inspiratory time as a fraction of total respiratory time. The PTI combines indicators of respiratory muscle strength and endurance and correlates directly with oxygen consumption and inversely with respiratory muscle fatigue. Clinically as muscle strength is depleted and muscle endurance can no longer sustain the workload

imposed upon it, the respiratory pump may begin to fail. PTI may be utilized to predict the onset of respiratory muscle fatigue.

PTI is calculated using pressure and flow measurements in conjunction with the inspiratory time fraction. The equation is as follows:

$$PTI = \left\{ \left[\sum (P_{EE} - P_{ES}) dt / T \right] \times T_i / T_{TOT} \right\} / MIP$$

P_{ES} = esophageal pressure

P_{EE} = end-expiratory esophageal pressure

dt = delta time

T = integration time (occurs during inspiration)

MIP = maximum inspiratory pressure during an occlusion maneuver

T_i/T_{TOT} = inspiratory time divided by total respiratory time

Another method is the tension–time index that utilizes the transdiaphragmatic pressure (P_{di}) measured from both gastric and esophageal balloons. In this method measurement of P_{es} and P_{ga} allows calculation of P_{di} according to the formula $P_{di} = P_{ga} - P_{es}$. Thus, the tension–time index for the diaphragm is the product of total respiratory cycle time and P_{di} /maximum P_{di} . The tension–time index has been correlated with oxygen consumed by the diaphragm and a value exceeding 0.15 is associated with diaphragm fatigue (Bellemare et al. 1983; Field et al. 1984). It should be noted that the concept of diaphragm fatigue is debated amongst respiratory physiologists but is beyond the scope of our discussion.

As previously stated a tension–time index or P_{TP} is reflective of work of breathing (WOB). Pressure waveforms can be obtained with the pneumotachograph at the airway and the area of the breath measured can subdivide the P_{TP} (Fig. 11.35). P_{TP} Area A is defined as the area of the pressure curve (integration of pressure with respect to time) from initiation of a breath to the beginning of ventilator pressurization. P_{TP} Area A reflects patient WOB since it reflects the effort by the patient during triggering. P_{TP} Area B is defined as the area of the pressure curve from the beginning of ventilator pressurization to return to baseline pressure. P_{TP} Area B reflects both patient and ventilator WOB. P_{TP} Area 1 is defined as P_{TP}

Area A plus P_{TP} Area B. P_{TP} Area 1 reflects initial work performed by both the patient and ventilator. P_{TP} Area 2 is defined as the area of the pressure curve during inspiration. P_{TP} Area 2 reflects work performed by the ventilator.

These calculations can be clinically relevant in regard to triggering the ventilator as discussed below.

11.9.3.8 Techniques and Limitations

Work of breathing performed by the patient on the respiratory system (physiologic work) and by the breathing apparatus (imposed work) during spontaneous ventilation is calculated by integrating changes in esophageal pressure, as an indirect measure of intrapleural pressure, and volume. This technique requires the placement of an airway pneumotachograph and an esophageal balloon. The esophageal balloon must be placed in the middle to lower third of the esophagus in order to best reflect changes in intrapleural pressure and not be affected by cardiac oscillations transmitted in the upper portions of the esophagus. To assure the esophageal catheter is in the correct position, a dynamic “occlusion test” is performed (Baydur et al. 1982; Milner et al. 1978). This test requires that the patient be spontaneously breathing so that an inspiratory effort is performed against a closed airway and then assessing that P_{es} changes correspond to changes in P_{AO} .

A limitation of this technique in mechanically ventilated patients is the availability of the necessary equipment to perform these measurements and calculations at the bedside. Unfortunately, integration of this equipment into the ventilator platform is currently limited to one ventilator manufacturer. Also important, the esophageal pressure displayed must be in good agreement with direct measurements of P_{pl} . MilicEmilie et al. (1964) demonstrated that total work may be inaccurate when inspiratory and expiratory works are estimated separately due to the overcompensation by expiratory work (Baydur et al. 1982).

Another limitation is seen in patients who display intrinsic PEEP where the placement of the chest wall relaxation curve on the Campbell

diagram is inaccurate because the work performed to overcome flow resistance of the chest wall is not accounted for accurately.

When calculating mechanical work, the site of measurement may impact its accuracy. Since mechanical work is traditionally calculated from volume changes at the mouth when the actual volume change occurs in the lung, this difference may be exaggerated in situations where there is airway obstruction, hyperinflation, or tachypnea. In these cases the mouth measurement underestimates the true work.

Finally, as discussed above, assumptions are made in the calculation of work of breathing regarding the respiratory system and its ability to follow the relaxation pressure–volume curve. When there are distortions of the chest wall due to high levels of ventilation and effort, the measured work may be again underestimated.

11.9.4 Clinical Relevance

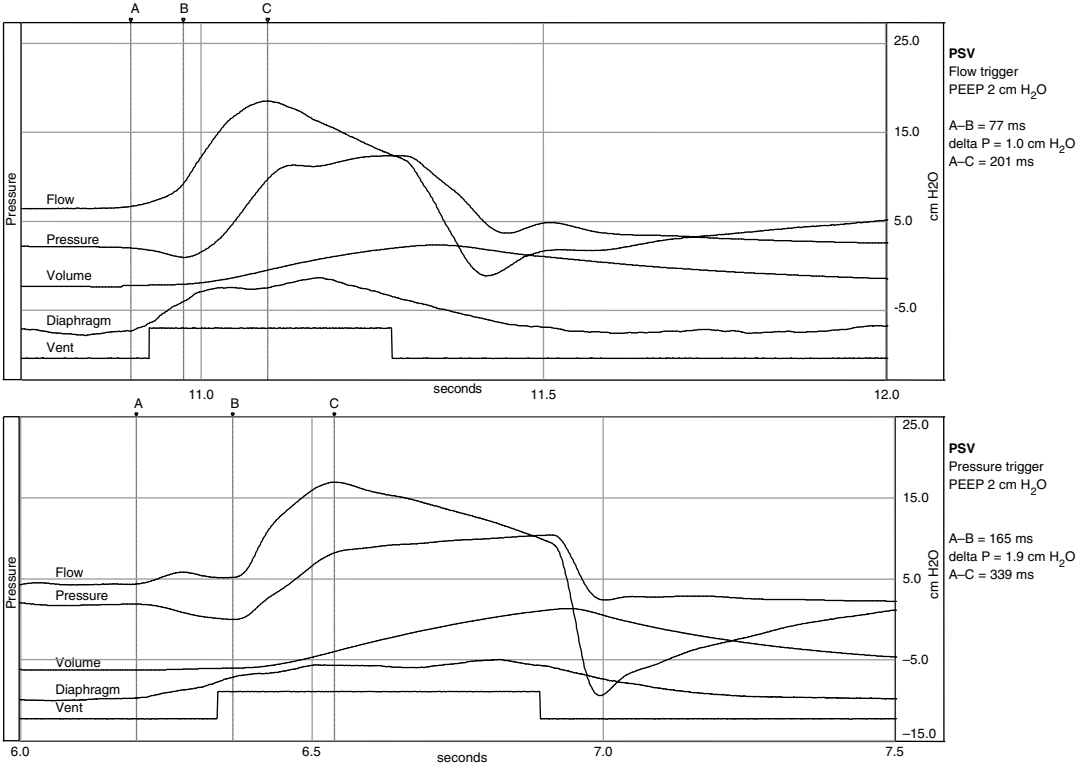
WOB is frequently discussed when physicians perform rounds on their patients in the intensive care unit, but applying actual measurements of WOB in clinical decision making has been elusive. Available evidence suggests that total unloading of respiratory muscles can allow the respiratory muscles to rest and recover (Braun et al. 1983; Stoller 1991). Goals of mechanical ventilation have been to reduce this work thus allowing recovery of respiratory muscles. However, this support must be balanced between causing muscle fatigue secondary to increased muscle loading from breathing through a high-resistance apparatus and resultant muscle atrophy due to totally unloading respiratory muscles for prolonged periods (Civetta 1993).

In order to balance the above factors, we must understand the variability of the work associated with different breathing apparatus. Figure 11.37 demonstrates associated imposed WOB with frequently used ventilators in neonatal and pediatric patients. This variability between ventilators is associated with a various aspects of ventilator design. As can be seen in Fig. 11.38, the associated WOB for the patient occurs predominately

during the trigger phase. Triggering in modern ventilators occurs in response to either a pressure or a flow signal. Both signals require the patient to initiate flow by a pressure drop across the endotracheal tube. The imposed WOB with flow triggering is less than with pressure triggering; however, the difference is primarily related to post-trigger events rather than triggering per se. It has been demonstrated that flow triggering in neonatal and pediatric patients decreases WOB (Carmack et al. 1995), as can be seen in Fig. 11.36 (Sanders et al. 2001). The advantage of flow triggering is associated with the decreased effort generated by the patient, as exemplified by both the reduced negative inspiratory pressure generated to trigger the ventilator and the response time of the ventilator (Giuliani et al. 1995). The response time of the ventilator is the time delay from the patient's effort to trigger the ventilator, as seen in Fig. 11.35, to the ventilator response indicated by opening of the inspiratory valve and the onset of fresh gas flow. This response can be affected by the triggering sensitivity setting (pressure or flow) and response characteristics of the ventilator demand system. As can be seen in Figs. 11.37, 11.38, 11.39, 11.40, and 11.41 the response time and effort necessary to trigger the ventilator can vary due to the certain design issues. First it relates to timing of the trigger signal. Ideally in flow triggering, the beginning of the signal should correspond to when inspiratory flow crosses the zero line. However, as can be seen in Fig. 11.39, there can be a delay between when this signal occurs and when the ventilator opens the inspiratory valve. Work is increased in this situation because during this phase of triggering, all effort is generated by the patient with no support from the ventilator.

In order to decrease the response time, it has been proposed to use a sensor at the patient's airway. In Fig. 11.42, three different types of airway sensors are compared demonstrating differences amongst different sensors with evidence of increased WOB and effort to trigger with the variable orifice sensor.

It is important to note that the rate and slope of the delivered flow can also have an effect on

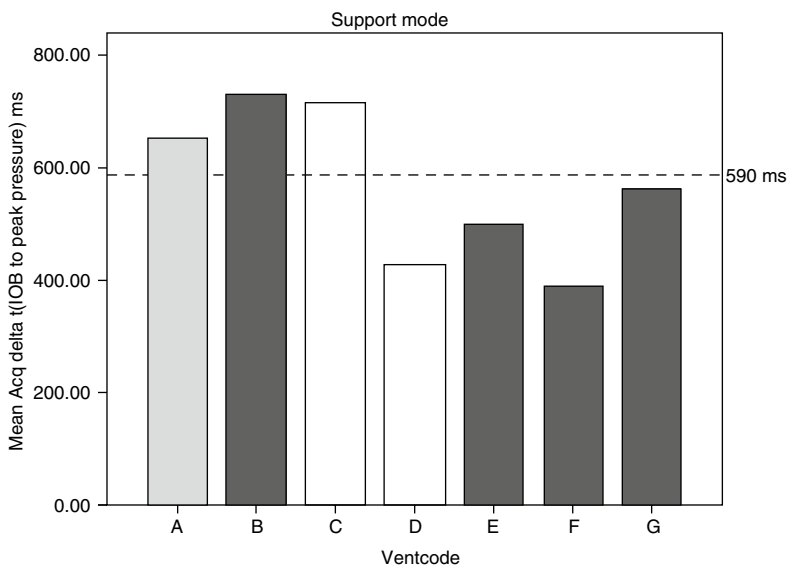


A = initiation of breath; B = most negative pressure; C = peak flow

Fig. 11.36 The *upper waveform* represents a single breath of a spontaneously breathing animal on pressure support being flow triggered. The *bottom waveform* represents a pressure-triggered breath. The negative pressure generated by the animal during triggering of the pressure-

triggered breath is almost double of the pressure necessary to trigger the flow-triggered breath. Also there is evidence of increased trigger delay in the pressure-triggered breath (Sanders et al. 2001)

Fig. 11.37 Represents the time in ms from the initiation of the breath, where flow crosses zero to the peak inspiratory pressure in seven modern ventilators. This area of the breath represents the total response time from initiation to full pressurization of the breath. The average time across the seven ventilators for animals breathing spontaneously is 590 ms with a range of 390–710 ms. *IOB* initiation of breath



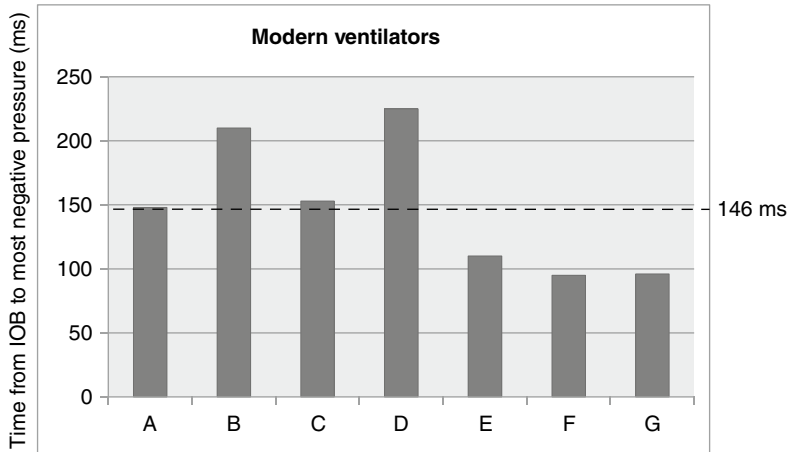


Fig. 11.38 Represents the time in ms from the point where the breath is initiated (where flow crosses the *zero line*) till point of the most negative deflection of pressure. The breath is measured from the beginning of the breath represented as the point when flow crosses zero till the point when the animal generates the most negative

deflection of pressure. This period of time represents the effort of the animal and corresponds to the work of breathing during triggering of the ventilator. This graph represents this measurement for 7 modern pediatric ventilators. The average time for these ventilators was 148 ms with a range of 97–220 ms. *IOB* initiation of breath

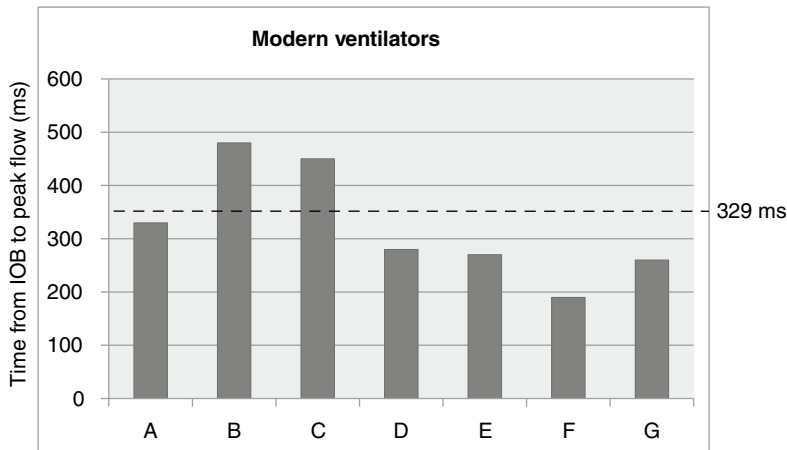


Fig. 11.39 Represents the time in ms from the point where the breath is initiated (where flow crosses the *zero line*) till point of maximum flow. The breath is measured from the beginning of the breath represented as the point when flow crosses zero till the point when the animal generates the peak inspiratory flow. This period of time repre-

sents the effort of the animal and corresponds to the work of breathing during entire triggering of the ventilator plus the time to complete pressurization. This graph represents this measurement for 7 modern pediatric ventilators. The average time for these ventilators was 329 ms with a range of 195–470 ms. *IOB* initiation of breath

the WOB. If flow is inadequate, then the patient effort to obtain flow from the ventilator system may be exaggerated due to high respiratory drive, thus increasing WOB. Modern ventilators allow the clinician to control the initial flow,

termed inspiratory rise time (Chatmongkolchart et al. 2001).

Investigators have examined the utility of predicting the outcome of weaning from mechanical ventilatory support by measuring the level of

Fig. 11.40 Represents the average sum of elastic and resistive work of breathing (j/l) for animals breathing on six modern ventilators during flow triggering. The average patient work of breathing is 0.65 j/l. The range of work of breathing for these ventilators are 0.5–0.92 j/l representing a twofold increase in WOB between ventilator B to ventilator A

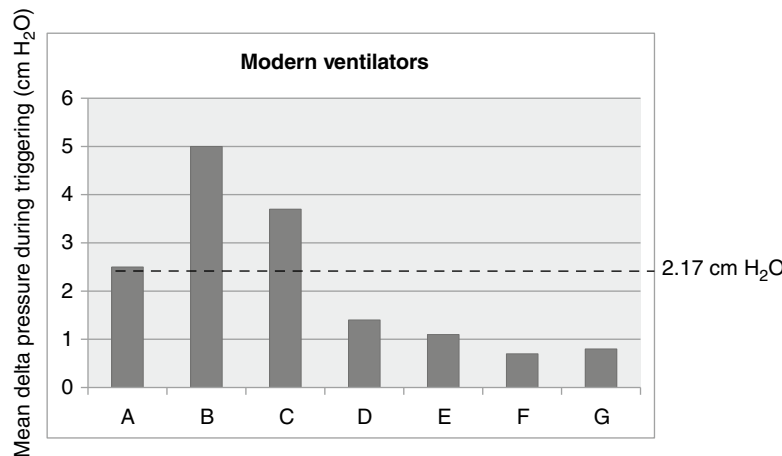
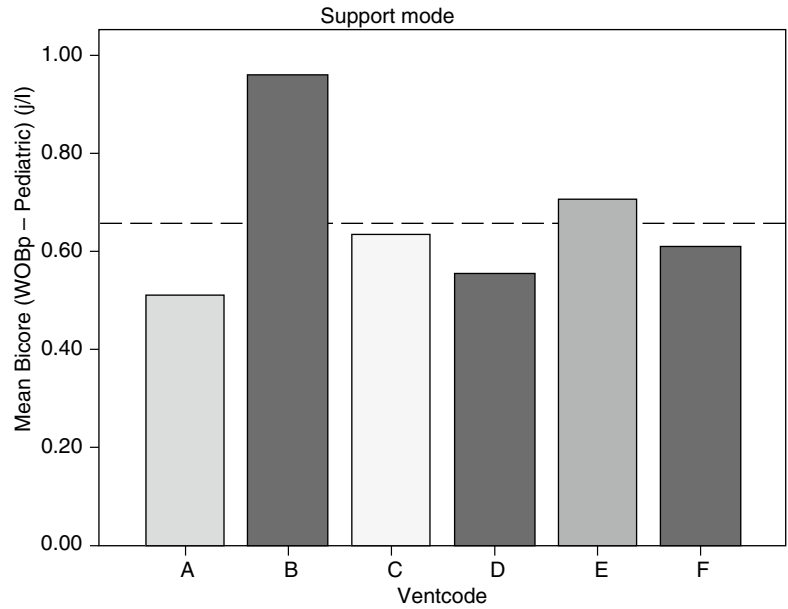


Fig. 11.41 Represents the amount of pressure generated by an animal breathing on a group of 7 pediatric ventilators during the trigger phase. The pressure generated is measured as the most negative deflection of pressure generated in cm H₂O for these ventilators. This measure rep-

resents the effort by the animal to trigger the ventilator and is a surrogate of the WOB generated by the animal during triggering. The average pressure generated was 2.17 cm H₂O with a range between the ventilators of 0.6–4.9 cm H₂O

inspiratory work. The predictive value of respiratory work as an index of weaning patients from mechanical ventilation remains to be determined (Marini et al. 1986).

11.9.4.1 WOB in the Pediatric Patient

Studies examining the use of WOB measurements as predictors of weaning or to perform accurate measurement of elastic, flow-resistive,

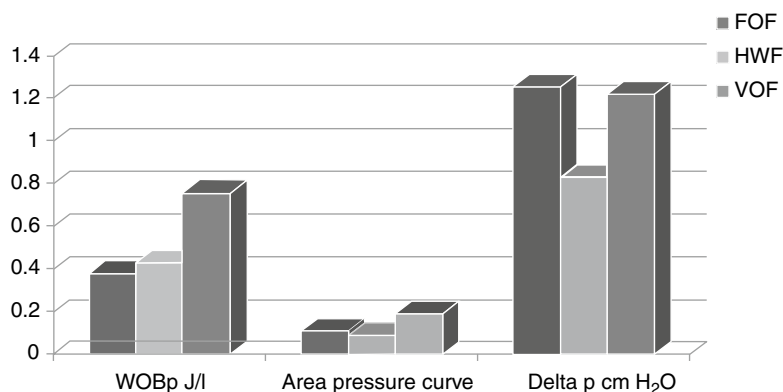


Fig. 11.42 Represents a comparison of three types of airway sensors in regard to the WOB (j/l), area pressure curve (see Fig. 11.6), and the pressure (cm H₂O) generated during the triggering phase representing the triggering effort. As can be seen in the figure, the VOF airway

sensor has the highest degree of WOB and effort by the animal. The airway sensors are a fix orifice airway sensor (FOF), heated wire airway sensor (HWF), and a variable orifice airway sensor (VOF)

and imposed work during mechanical ventilation to guide the level of support or to guide specific selection of the ventilator mode are limited in pediatric patients. In adult patients the best measure of WOB was measured work on the lungs via measurement of transpulmonary pressure and flow. However, the threshold value for differentiating patients who were ventilator dependent from those who were ventilator independent differs between reported studies, limiting their application to clinical practice. Reported studies in adults have not included large randomized series with WOB measures utilized in a prospective manner, thus further limiting the ability to apply reported values to decision making by clinicians. Pediatric studies of work of breathing have demonstrated that the level of WOB is associated with the level of support. In pediatric patients there is the problem of large instrumental dead space (Dassieu et al. 1998). Patel et al. reported in 20 infants that the mean transdiaphragmatic pressure–time product was higher with volume targeting at 4 ml/kg in comparison with a baseline of 6 ml/kg, regardless of the patient-triggered mode (Patel et al. 2009). This study implies that there is a minimal level of support

required for infants to deal with the increased resistive work associated with breathing on a mechanical ventilator but does not offer insight into using P_{TP} as a predictor of weaning. Another study of pediatric patients has noted that for children with peripheral airway obstruction who require assisted ventilation, work of breathing during spontaneous breaths is decreased by the application of either compensatory positive end-expiratory pressure or pressure support (Graham et al. 2007). The type of trigger may have an effect on WOB (Sasson et al. 1994). However, Thiagarajan et al. demonstrated in pediatric patients that flow triggering might only reduce WOB when lung compliance is decreased (Thiagarajan et al. 2004). Even though these studies may offer insight into how the clinician can compensate for the higher instrumental dead space in pediatric patients and the effect on WOB, further study is required to examine if WOB measurements can be integrated into an algorithm for directing mechanical ventilations. It should be noted that any computer-driven system, even if it integrates data concerning WOB, may not outperform a team of dedicated intensivists and respiratory therapists (Laghi 2008).

11.9.4.2 WOB in the Neonatal Patient

Even more so than in the pediatric patient, measurement of WOB in the neonatal patient remains largely a research tool. Accurate measurements are technically difficult and subject to error in intubated patients due in part to the leak around the uncuffed endotracheal tube. Other problems with measurement, discussed under *Techniques and Limitations*, above, also apply.

As previously described, inspiratory work can be calculated from P_{es} and volume recordings in the spontaneously breathing patient ($P_{aw}=0$). Accuracy is increased in the non-intubated patient where effect of the endotracheal tube and associated leak is not an issue. Such measurements have been done in studies of noninvasive respiratory support such as continuous positive airway pressure (Pandit et al. 2001) using calibrated respiratory inductance plethysmography (RIP) to measure volume changes. Even so, these measurements are technically challenging and difficult. Calibrated RIP is certainly possible for volume measurements in the intubated patient, but accurate calibration is difficult.

Assessment of phase angle from RIP rib cage and abdominal bands can be used to estimate increases or decreases in WOB. The phase delay between expansion of the abdomen and rib cage can be expressed in degrees, with phase angles of 0° representing in-phase rib cage and abdominal movements and 180° representing totally out-of-phase movements. These measurements can be useful as they do not require calibration of the RIP signal and have been reported in evaluations in preterm infants (Chang et al. 2011).

The Campbell diagram has been used to quantify WOB in neonates (Jarreau et al. 1996). When effort is made to quantify the leak around the ETT, account for dead space of the pneumotachograph, and accurately calibrate the equipment, these measurements can be useful. WOB values calculated by some current neonatal ventilators may be useful for trending values but may not be accurate given problems with leak and possibilities of inaccurate calibration.

Transdiaphragmatic pressure–time product, described earlier in this chapter, has also been

used to estimate WOB in neonates (Patel et al. 2010). These measurements, also, are time intensive and require sensitive equipment and accurate calibration for useful results, thus relegating them predominantly to research tools.

At this time, probably the most useful evaluation of WOB in the infant remains clinical assessment of breathing pattern. Increasing tachypnea and associated retractions or “abdominal” breathing should always alert the caregiver to increased WOB requiring careful assessment of cause and possible treatment options.

Future Perspectives

The use of work of breathing measurements to affect direct patient care during mechanical ventilation has been limited by the invasive nature of these measurements, which require an esophageal balloon and a freestanding monitor. Accurate measurement of elastic, flow-resistive, and imposed work during mechanical ventilation may be advantageous to the clinician in order to monitor ventilatory interventions that may optimize respiratory muscle loading and decrease the work of breathing. It has been demonstrated that the best predictor is a measure of the work performed by the lungs via measurement of transpulmonary pressure and flow. Further, the efficiency of these measurements in adults appears to be best predictive in ventilator-dependent patients. Recent technological advances have revived interest in utilizing an esophageal catheter to allow measurement of the patient’s diaphragmatic EMG signal to trigger the ventilator and direct the level of ventilatory support. Future development needs to integrate esophageal manometry to measure respiratory work into these systems as part of available measures assisting the clinician in weaning and successful extubation. Further, any future studies must utilize these measurements in a prospective manner in large randomized trials.

Essentials to Remember

- Work of breathing can be subdivided into the work necessary to overcome the resistive, elastic, and inertial components and the work to move the chest wall and intestinal organs.
- WOB can be subdivided into work attributed to the patient (physiologic WOB, WOB_p) and that associated with the ventilator (imposed WOB, WOB_v).
- It is essential in order to clinically apply measurements of WOB to not only differentiate the patient and ventilator components but also those associated with the work necessary to overcome the resistive and elastic components.
- In the case of ineffective respiratory effort, when muscle contraction occurs without volume displacement, traditional measurement of WOB cannot be measured since this calculation is based on volume displacement. A measure that appears to more closely approximate oxygen cost of breathing or energy expenditure of the muscles as a measure of work of breathing is the pressure–time product (P_{TP}).
- Goals of mechanical ventilation have been to reduce WOB, thus allowing recovery of respiratory muscles. However, this support must be balanced between causing muscle fatigue secondary to increased muscle loading from breathing through a highly resistive apparatus and resultant muscle atrophy due to totally unloading respiratory muscles for prolonged periods.

Educational Aims

After reading this chapter, the reader will be able to:

- Describe the main respiratory monitoring tools available for all physicians taking care of critically ill children.
- Titrate therapeutic interventions to the patient's disease state in order to provide optimal respiratory support and aid in eventual weaning to endotracheal extubation.
- Understand the potential role for rational respiratory monitoring in future pediatric trials involving mechanical ventilation.

11.10.1 Introduction

Respiratory failure is one of the most common reasons for admission to pediatric intensive care units (PICUs), particularly in the first 2 years of life. While patients are recovering from the etiology leading to respiratory collapse, intensivists are charged with supporting the respiratory system with mechanical ventilation. Fundamental to ensuring adequate support is close supervision of therapeutic interventions – through both invasive and noninvasive forms of respiratory monitoring. This discussion concentrates on common means of respiratory monitoring used in intensive care units. In particular, when mechanical assistance to ventilation is required, its optimal use demands that the user understands the relationship between the mechanical device and the mechanical properties of the patient's respiratory system so that optimal gas exchange can be provided. It is probable that the minimum physiological information needed for rational monitoring providing for the successful use of a mechanical ventilator requires understanding of at least five parameters: alveolar partial pressure of CO_2 ($PACO_2$), arterial oxygen saturation (SaO_2), the mechanical RC (resistance–compliance) time constant, functional residual capacity (FRC), and pressure–volume loop (PV) characteristics (Shannon 1989;

11.10 Respiratory Monitoring of the Mechanical Behavior of the Respiratory System During Mechanical Ventilation: Clinical Application

Christopher J.L. Newth and Robinder G. Khemani

Hammer and Newth 1995). However, not all of these techniques need to be applied to all infants and children ventilated in the ICU.

11.10.2 Gas Exchange

Regardless of the process leading children to require mechanical ventilation, the pediatric intensivist wishes to maintain gas exchange to keep the body in a state of relative homeostasis. Gas exchange will be discussed elsewhere in this book, but the continuous monitoring of gas exchange with both invasive and noninvasive measures of oxygenation and ventilation is fundamental to computer-based decision support tools for automation of ventilator management and weaning to extubation (see Chap. 12).

11.10.3 Work of Breathing Measurements

In addition to normalizing gas exchange, another important goal of mechanical ventilation is to support patients while they are recovering from the inciting event that led to respiratory failure. To this end, minimizing work of breathing (WOB) during recovery by optimal selection of ventilator support allows the patient the highest likelihood of weaning to extubation. This is particularly useful for patients with obstructive airway disease.

11.10.3.1 Esophageal Manometry

Esophageal manometry has long been used in animals and adults to study the mechanics of breathing. An esophageal manometer can be used to subdivide measurements of respiratory system compliance into contributions from the chest wall and those from the lung. Respiratory system work is the pressure applied to yield a change in volume of the system. In reality, this work is comprised of elastic, resistive, inspiratory, expiratory, lung, and chest wall components (Benditt 2005). The most significant and dynamic component of work of breathing is best estimated by the change in pleural pressure needed to gener-

ate a change in volume. A liquid- or air-filled esophageal manometer, placed correctly in the lower third of the esophagus (Coates et al. 1989; Jackson et al. 1995), closely approximates pleural pressure (Asher et al. 1982; Higgs et al. 1983).

Esophageal manometry can monitor patient-initiated work on various levels of support (Graham et al. 2007). A good example of this is having a spontaneously breathing patient on continuous positive airway pressure (CPAP) and pressure support (PS) where optimal ventilator support is titrated based on the patient's WOB and comfort. Modern ventilators increasingly have built-in software to analyze WOB when paired with an esophageal catheter. This has led to further investigations of this type of monitoring, with recent contributions in the areas of prediction of extubation outcome (Harikumar et al. 2009) and selection of appropriate PEEP in acute lung injury and respiratory distress syndrome (Talmor et al. 2008; Loring et al. 2010).

11.10.3.2 Respiratory Plethysmography

During normal tidal breathing, without significant pathology, diaphragm contraction leads inspiration followed quickly by chest wall muscle activity. However, as respiratory pathology develops, regardless of etiology, there is often an increasing amount of thoracoabdominal asynchrony (TAA), resulting from worsening respiratory (initially intercostal) muscle fatigue. Such TAA can be measured using respiratory plethysmography (Ross et al. 2010; Sivan et al. 1990; Hammer and Newth 2009).

Elastic bands are placed around the rib cage (RC) and abdomen (ABD) at the nipple line and umbilicus level, respectively. The output of these movements is then downloaded to a computer program that displays characteristic oscillatory patterns which approximate sine waves. The level of synchrony between these two bands, the phase angle (Θ), is then calculated as

$$\sin \Theta = m / s$$

where m is the length of the midpoint of the RC excursion and s is the length depicting the ABD excursion (Rossi et al. 1985b).

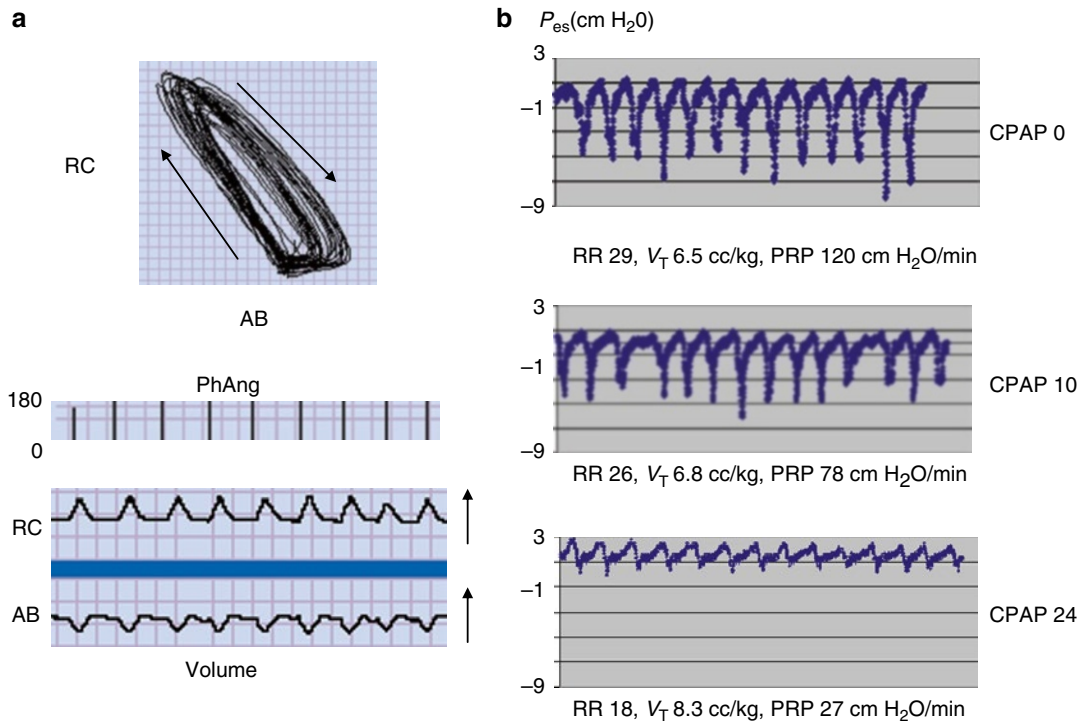


Fig. 11.43 Plethysmographic and esophageal pressure tracings during spontaneous breathing in a child with bilateral diaphragmatic paralysis. (a) *Top panel*, Konno-Mead plot of abdominal excursion (AB) against rib cage (RC) excursion. *Middle panel*, graphic representation of phase angle (PhAng) with each breath. *Bottom panel*, simultaneous plethysmographic waveforms over time. (b) esophageal pressure (P_{es}) tracings from the same child at increasing levels of continuous positive airway pressure

(CPAP), with associated tidal volume (V_T), respiratory rate (RR), and pressure-rate product (PRP). During the course of increasing CPAP, in this situation, the phase angle and its clockwise rotation remain unchanged, but the pressure-rate product declines. This strongly suggests the diaphragms have become “medically plicated” by the increased CPAP and breathing has become more efficient (Reproduced with permission – *Pediatr Crit Care Med*. 2004)

During normal breathing, the phase angle is less than 22° (mean 8°) and creates a very tight, counterclockwise loop (Sivan et al. 1991). However, as TAA worsens, the loop opens and widens, with larger phase angles. Additional information is learned from the direction of rotation of the loop. If the RC leads instead of the ABD, then the loop will take on a clockwise rotation, commonly seen with bilateral diaphragm paralysis. If one hemidiaphragm or hemithorax is ineffective, the loop will take on a “Figure of 8” appearance. As such, continuous phase angle monitoring allows clinicians to see the effect of medical interventions (e.g., increased CPAP), monitor disease progression (e.g., acute upper airway obstruction),

and help wean from mechanical ventilation (Fig. 11.43).

11.10.4 Monitoring Respiratory Mechanics

Ventilator management of respiratory failure needs to cater to the underlying disease pathology. Paramount to optimal management is not only initially selecting the correct mode and ventilator settings for the underlying disease but also monitoring physiologic changes that occur from the disease state or in response to therapeutic interventions. Most modern ventilators will display pressure, flow, and volume traces on a

time basis or will display plots of the variables against each other. The ventilator will also calculate values for resistance, compliance, and time constant of the respiratory system it is supporting in addition to air leak (hopefully only around the endotracheal tube), tidal volumes, and so on.

11.10.4.1 Resistance, Compliance, and Time Constant

Compliance and resistance reflect the mechanical properties of the lungs and require the measurement of flow, volume, and pressure.

Compliance is a function not only of the elastic properties of the respiratory system but also of its volume. In other words, the value obtained is different at various lung volumes, dependent on the shape of the pressure–volume curve, which in turn depends on the amount of lung disease and therapeutic maneuvers such as PEEP or surfactant administration. Sudden changes in compliance often reflect the opening and closing of individual lung units rather than changes in lung tissue and surface tension characteristics. Thus, ideally compliance should be corrected for total lung capacity (TLC) and body weight. Compliance referenced to functional residual capacity (FRC) is termed specific compliance.

Resistance represents the resistive properties of the airways, lung tissue, and chest wall. Several methods have been designed to measure compliance and resistance in ventilated infants which has led to a confusing nomenclature for the practitioner. Compliance is referred to as either dynamic compliance (C_{dyn}) when it is measured when ventilation is in motion or as static (passive) compliance (C_{rs}) when respiratory muscles are inactive during the test procedure. The same applies to the resistance of the respiratory system, which is referred to as either dynamic (R_e) or total respiratory system resistance (R_{rs}). C_{dyn} can be calculated simply by dividing V_T by the total change in pressure necessary to deliver that volume. These numbers can be easily extracted from modern mechanical ventilators. However, it is understood that C_{dyn} is related to both elastic and flow-resistive

characteristics according to the equation of motion of the single-compartment model of the respiratory system. Thus, C_{dyn} changes with alteration of mechanical ventilation settings including respiratory frequency, inspiratory, and end-expiratory pressure. The classic technique of determining C_{dyn} is based on the measurement of esophageal pressure as a quantification of pleural pressure. This technique is invasive by virtue of the need of an esophageal catheter, and the accuracy of such measurements in intubated infants and children is controversial.

Newer methods measure static compliance (C_{rs}) and resistance (R_{rs}) and are based on relaxation of both inspiratory and expiratory muscles during brief airway occlusions during exhalation. The most widely used methods are the passive deflation and the multiple occlusion techniques. Muscle relaxation is achieved either by invoking the Hering–Breuer inflation reflex or by use of neuromuscular blockade. We favor the use of short-term neuromuscular blockade together with sedation for a mechanically ventilated patient in the controlled setting of an ICU because it guarantees complete muscle relaxation during the whole expiratory phase. If there is no muscle activity during exhalation, the expiratory time constant (T_{rs}) or emptying time of the respiratory system will be entirely dependent on the mechanical properties of the lungs and can be described as follows:

$$T_{\text{rs}} = C_{\text{rs}} \times R_{\text{rs}}$$

Thus, both C_{rs} and R_{rs} can be obtained from a single breath. The determination of T_{rs} gives some idea of how rapidly the lung empties following a mechanical breath. A single time constant is defined as the time required to exhale 63 % of the tidal volume. Four time constants are needed to exhale 99 % of the delivered tidal volume. This permits the determination of respiratory rates allowing complete exhalation or the detection of rate settings that lead to inadvertent PEEP (Fig. 11.44).

In the examples above, the most likely situation where the “equilibrium” time constant

Ventilated 3.5 mm ID ETT 5 kg infants	Healthy (normal)	ARDS (restrictivel)	Bronchiolitis (obstructive)
R (cm H ₂ O.L ⁻¹ ..s ⁻¹)	50	100	600
C (L.cm H ₂ O ⁻¹)	0.006	0.0015	0.003
RC (s)	0.03	0.15	1.8
4RC (s)	1.2	0.6	7.2
60 / (4*RC) = (fmax.min ⁻¹)	50	100	8

Fig. 11.44 The estimated maximum respiratory frequency calculated from the RC time constant of the respiratory system to prevent breath stacking with overdistension of the lungs, in infants with three different

pulmonary states – normal, restrictive pulmonary disease, and obstructed airways disease. In this model, it is assumed that the inflation of the lungs occurs instantly and only the time required for deflation is determined

(4*RC) will be exceeded is in the case of bronchiolitis. When this happens, there will not be enough time for all the previous tidal volume to be exhaled before the next breath starts, resulting in an elevation of functional residual capacity (FRC). This can result in barotrauma if the elevation becomes more than 20 ml/kg, in the case of adults with asthma (Fig. 11.45) (Tuxen et al. 1992).

Pattern recognition adds valuable information to the interpretation of results obtained by measuring respiratory mechanics. While obstructive lung disease is characterized by a concave slope of the passive expiratory FV loop, restrictive lung disease often results in convex loop patterns. It is important to note that in the case of intubated patients, respiratory system compliance (C_{rs}) and resistance (R_{rs}) measurements include the physical properties of the ETT. Unfortunately, there is still a lack of normal values for C_{rs} and R_{rs} in intubated infants and children with normal lungs. According to our studies, such normal data lie in the range of 0.8–1.2 ml·cm H₂O⁻¹·kg⁻¹ for compliance and 0.02–0.05 cm H₂O·ml⁻¹·s⁻¹ (up to 0.1 with ETT <3.5 mm I.D.) for resistance (Hammer et al. 1995).

11.10.4.2 Loops Using Pressure, Flow, and Volume Traces: Special Considerations

11.10.4.2.1 Precision of Measurements

Before discussing characteristic patterns of various loops for different disease states, it is necessary to review the accuracy and reproducibility of these measurements. The presence of a significant leak (>18 %) around the ETT will underestimate returned tidal volumes and increase calculated resistance and compliance values (Main et al. 2001). This is easily overcome with a cuffed ETT. While there is reluctance by some of the critical care and anesthesia community to use cuffed ETTs for pediatric patients, good data shows that current low-pressure, high-volume cuffed tubes are no different than uncuffed tubes in the incidence of acute or long-term postextubation complications (Newth et al. 2004). As with uncuffed ETTs, cuffed tubes should be placed with an initial leak at less than 25 cm H₂O.

Second, in order to obtain accurate flow–volume and pressure–volume loops, as well as measurements of tidal volume, it is important for measurements to occur as close to the tip of the ETT as possible. While modern ventilator

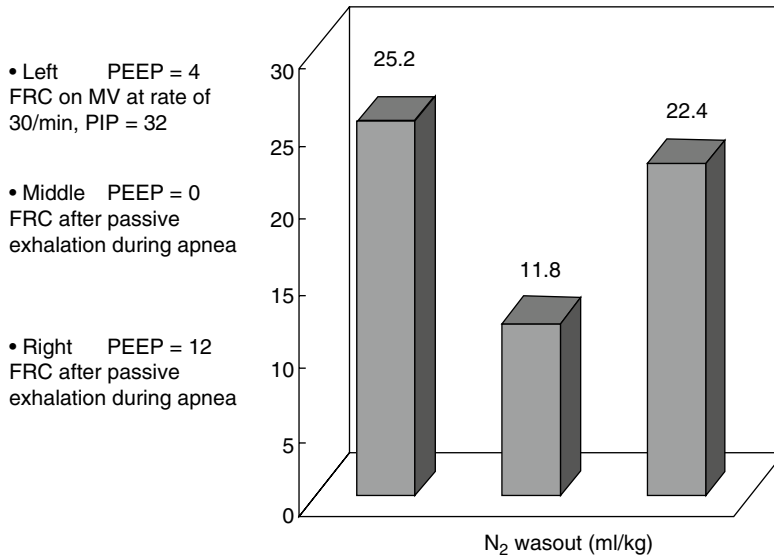


Fig. 11.45 These are measurements from an 8 kg infant with RSV bronchiolitis plus severe chronic lung disease. In the *left column*, his FRC has been measured at 25.2 ml/kg while on a ventilator rate of 30 breaths/min. When his FRC was repeated after 40 s apnea and PEEP=0 cm H₂O (*middle column*), it was only 11.8 ml/kg, reflecting that the increased rate (with a deflation time greater than

4*RC) had caused air trapping of approximately 13 ml/kg. The *right column* shows that even when his PEEP was raised to 12 cm H₂O, after an apneic deflation of 40 s, his FRC at 22.4 ml/kg was still less than originally at 25.2 ml/kg secondary to the “breath stacking” with the high ventilator rate

technology has improved significantly, there are often large discrepancies between measurements taken at the tip of the ETT with a pneumotachograph, and those recorded at the ventilator, regardless of the software package in use. This is particularly relevant with smaller patients, where the relatively compliant ventilator tubing dead space volume may be greater than a small patient’s tidal breath (Heulitt et al. 2009b).

11.10.4.2.2 Flow–Volume Loops

Flow–volume loops are particularly useful in diagnosing the type of respiratory disease present (restrictive versus obstructive). In the case of lower airway obstruction, they have a characteristic shape which may change in response to bronchodilators. In large airways (i.e., above the carina) they can help identify the type of obstruction (fixed or variable) if obtained while spontaneously breathing or if the ETT lies above the level of obstruction.

For mechanically ventilated patients, loops vary depending on the mode of ventilation selected. In volume ventilation, tidal volume delivered is set with a constant inspiratory flow, and peak and plateau airway pressures vary. In pressure ventilation, inspiratory pressure delivered is set and volume varies; the flow pattern is decelerating. In general, this decelerating flow pattern yields lower peak inspiratory pressures than volume limited ventilation.

It is necessary to understand the scales and axes when interpreting flow–volume loops on ventilators and those of usual pulmonary function testing. Classically, flow–volume loops produced by spontaneously breathing patients have inspiration negative, and exhalation positive, moving either clockwise or counterclockwise. However, the display on most mechanical ventilators shows the flow pattern is in a clockwise direction and inspiration is on the positive aspect of the y-axis and exhalation on the negative (Figs. 11.46 and 11.47).

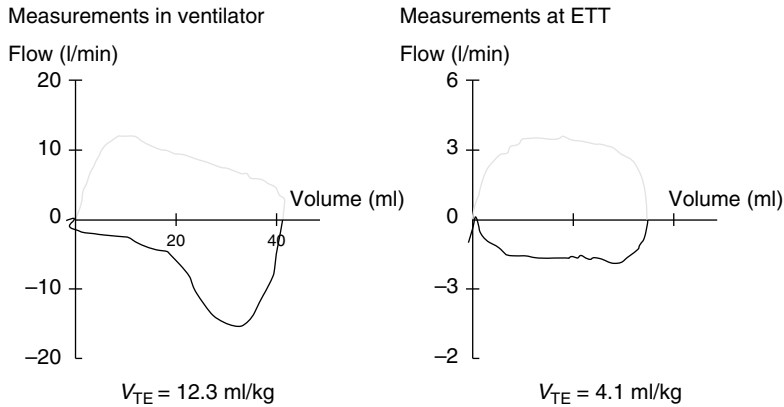


Fig. 11.46 Measurements from a 4.0 kg infant with a cuffed endotracheal tube in pressure control mode. On the left, flow–volume measurements are made at the ventilator with compensation for tubing compliance. There is “overshoot” of flow measurements causing volumes to be larger and giving the expiratory portion of the flow–volume curve (below the *horizontal axis*) a pattern of obstructive

airways disease. Tidal volume is 12.3 ml/kg. On the right, measurements are made at the endotracheal tube connector within a minute of those from the *left panel*. Tidal volume is much lower being now a third at 4.1 ml/kg. The flow pattern on the expiratory limb now resembles that of normal airways

11.10.4.2.3 Pressure–Volume Loops

Pressure–volume loops are useful to help determine optimal lung recruitment, compliance, and overdistension. Here, pressure is on the *x-axis*, and volume on the *y-axis*, a reversal of classic nomenclature.

11.10.4.2.3.1 Restrictive Lung Disease

Restrictive lung disease from pneumonia, ARDS, pleural effusions, and similar entities constitutes the majority of ICU admissions for respiratory failure. The hallmarks of restrictive lung disease include decreased compliance, with end-expiratory lung volumes that fall below normal functional residual capacity (FRC). Moreover, alveolar closing pressures lie above end-expiratory lung volume resulting in alveolar collapse. Therefore, effective management of restrictive lung disease requires normalization of end-expiratory lung volumes to a level closer to FRC. The pressure–volume curve helps to this end (Fig. 11.48).

The inspiratory limb of the pressure–volume curve of a patient with restrictive lung disease (classically ARDS) has three main segments, separated by upper and lower inflection points (see Fig. 11.25). The goal is to maintain venti-

lation within the two inflection points on the pressure–volume curve. This minimizes ventilator-induced injury from alveolar recruitment and derecruitment (below the lower inflection point) and overdistension (above the upper inflection point). End-expiratory lung volumes are maintained above the lower inflection point with positive end-expiratory pressure (PEEP) or by mean airway pressure if on high-frequency oscillatory ventilation.

While recommendations differ for conventional ventilation, one strategy is to select a PEEP 2 cm H₂O above the lower inflection point and attempt to stay in the zone of best compliance by selecting a relatively conservative tidal volume (6 ml/kg) if using a form of volume control ventilation (ARDSNet 2000) or use lung-protective pressures if applying a pressure control mode (Khemani et al. 2009). A third option is high-frequency oscillatory ventilation providing very small tidal volumes between the upper and lower inflection points.

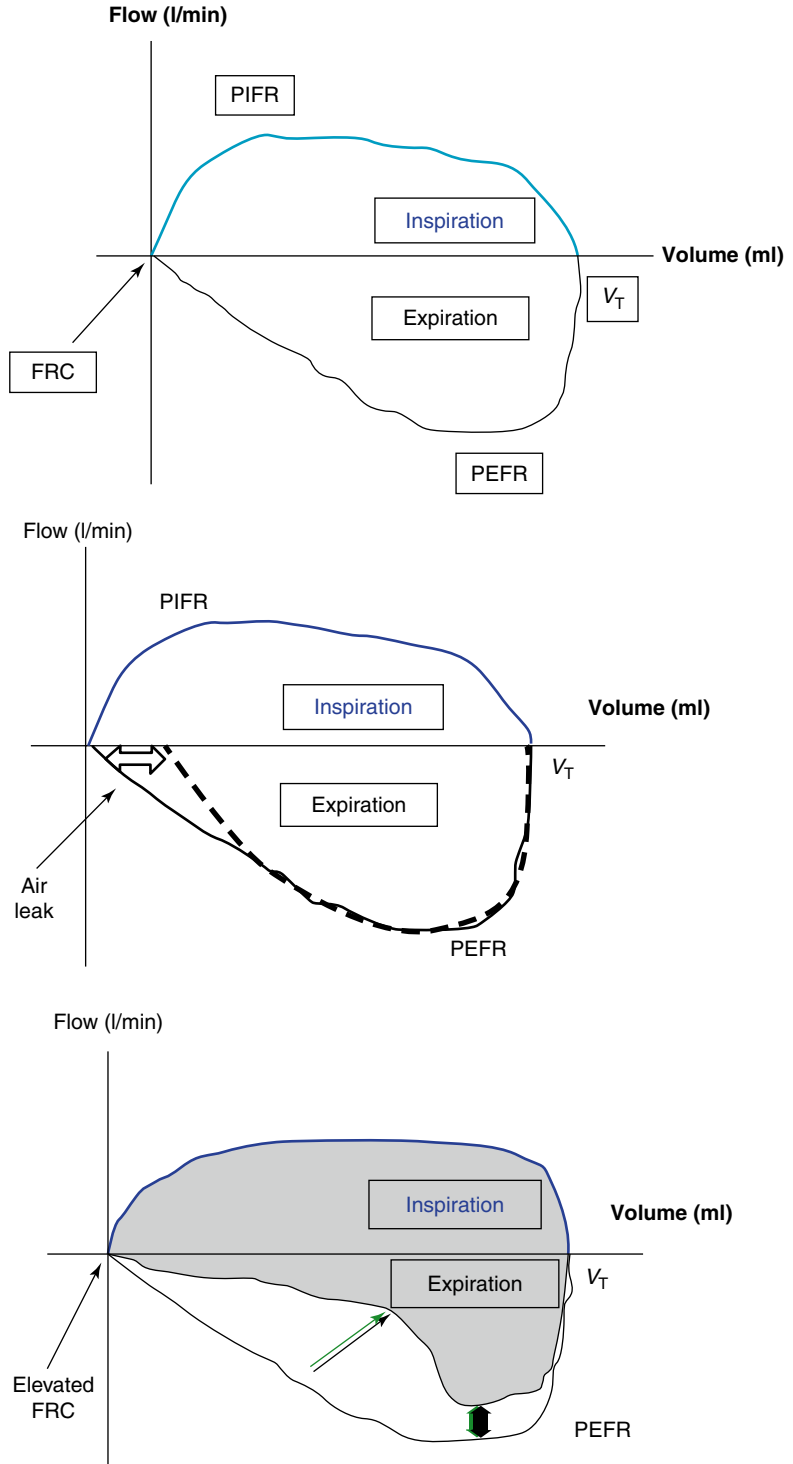
If a low compliance zone is seen on the pressure–volume curve (beaking), then the pressure or volume should be decreased to prevent overdistension. Less commonly, overdistension

Fig. 11.47 These are flow–volume loops under three different conditions.

Upper panel – normal healthy airways. *PIFR* peak inspiratory flow rate, *PEFR* peak expiratory flow rate, *FRC* functional residual capacity, V_T tidal volume.

Middle panel – the expired volume does not come back to the starting point (*FRC*) of the inspired volume. This means there is an air leak in the system, usually around the endotracheal tube.

Lower panel – obstructed airways disease. When severe enough, the classic scooped-out expiratory limb will be seen on tidal breaths on a ventilator. Note that *PEFR* will also be reduced, and the *FRC* (end-expiratory lung volume) will be higher in this case



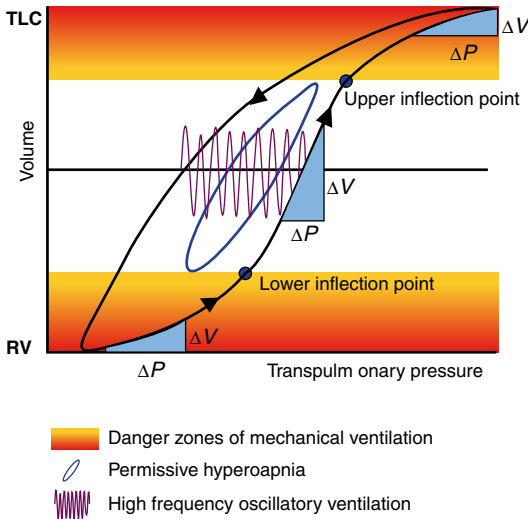


Fig. 11.48 A schematic of a pressure–volume loop in acute lung injury, demonstrating upper and lower inflection points. In between these points is the “safe” range in which to ventilate without moving in to the upper zone of overdistension or the lower zone of atelectasis. The compliance ($\Delta V/\Delta P$) in both “danger” zones is low, whereas it is improved in the “safe” zone (Reproduced with permission Prof. Jürg Hammer, Universität Basel, CH)

from excessive PEEP may occur. This will not manifest with the classic inflection points but rather simply as a pressure–volume curve that is shifted to the right with a smaller slope. Further disease entities and therapies which will result in changing respiratory system compliances are shown in Fig. 11.49.

Other measures of overdistension derived from mathematical examination of the pressure–volume curve have been proposed (Fig. 11.50).

In neonates, Fisher et al. (1988) noted that if the ratio of the compliance of the last 20 % and full PV loop is less than 1.0, overdistension is defined (Fig. 11.50). This definition has not been validated in the pediatric population (Neve et al. 2001). An alternate approach is that of Leclerc and colleagues who applied second-order polynomial equations to quasistatic PV curves and derived indices they showed suitable for detecting overdistension in pediatric patients (Neve et al. 2000, 2001).

In contrast to the pressure–volume curve, the flow–volume loop for a patient with significant restrictive lung disease will often have the

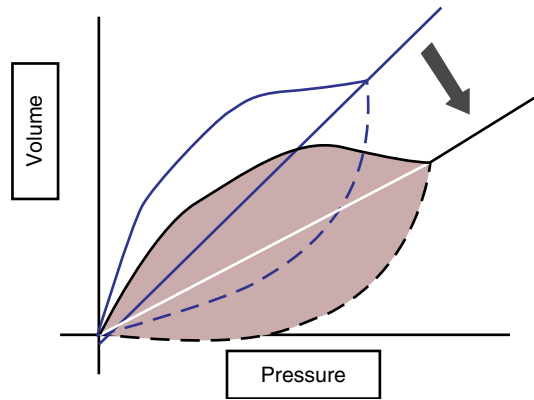


Fig. 11.49 A schematic of two pressure–volume loops. The upper PV loop with the greater slope represents either a normal loop which moves toward the lower loop with the smaller slope, as the lung becomes less compliant as in hyaline membrane disease or acute respiratory distress syndrome. Conversely, the lower loop will move toward the upper one as compliance improves, such as with surfactant therapy for HMD or recruitment maneuvers with ARDS

same characteristic shape as a patient without lung disease, but with smaller amplitude for a given flow. Subsequent to changes in compliance through optimizing PEEP and improvements in the underlying disease, in concert with conservative lung-protective pressure-limited ventilation, the amplitude of the flow–volume loops should return toward normal.

11.10.4.2.3.2 Obstructed Airway Disease Medium and Small Airway Disease

In contrast to restrictive lung disease where disease pathology typically affects the lung parenchyma, obstructive disease affects airways. Significant airway obstruction affecting medium (asthma) or small (bronchiolitis) airways allows the development of air trapping. Here end-expiratory lung volumes tend to reside above functional residual capacity, and airway resistance is increased. The flow–volume loops are characteristic of flow limitation on the expiratory limb. The flow–volume loop therefore demonstrates lower peak expiratory flows, smaller tidal volumes, as well as the hallmark “scooped-out” or concave appearance to the deflation limb of expiratory flow. Moreover, if the obstruction is variable or reversible, the effect of a therapeutic

Fig. 11.50 A schematic of a pressure–volume loop demonstrating overdistension. On the pressure axis, between 0.8 and maximum pressure (X), there is very little change in volume (Y). This region has very low compliance and results in “beaking” of the upper end of the PV loop

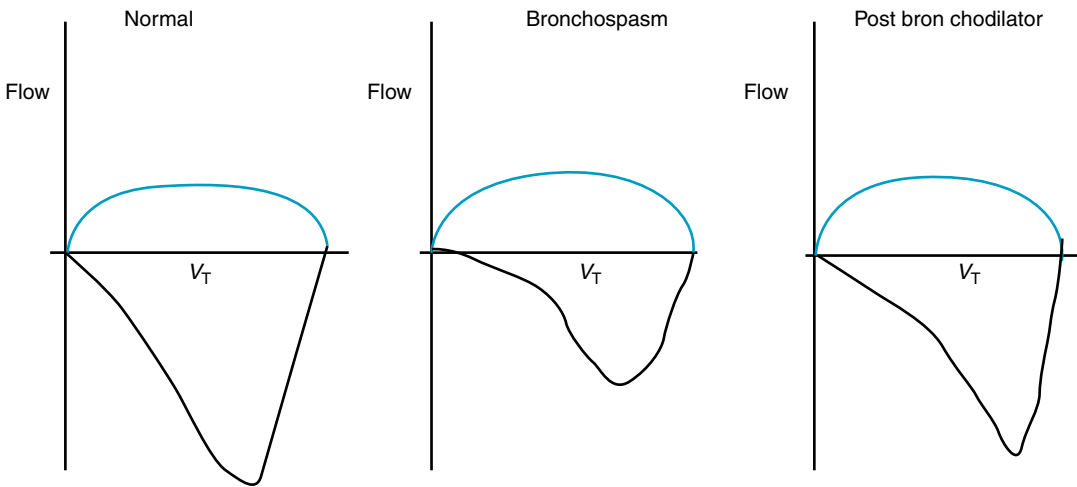
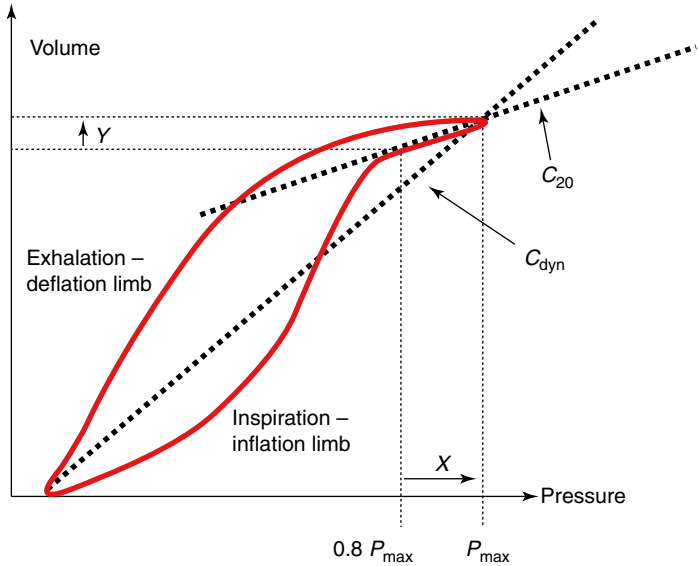


Fig. 11.51 A schematic of 3 flow–volume loops demonstrating the following: *Left panel* – normal loop. *Middle panel* – bronchoconstriction with concavity of the deflation limb, decreased peak expiratory flow rate, and decline

in tidal volume (V_T). *Right panel* – response to bronchodilator with improvements in tidal volume, peak flow, and less concavity of the deflation limb

intervention (i.e., bronchodilator for an asthmatic) can be followed. Here the flow–volume loop demonstrates improved peak expiratory flow and a return of a flat or slightly convex shape to the decelerating limb of expiratory flow. Some modern ventilators allow reference flow–volume and pressure–volume loops to be stored on the ventilator screen so that subsequent loops can be superimposed and changes in shape after an intervention such as a bronchodilator can be appreciated (Fig. 11.51).

When mechanically ventilating patients with significant obstructive airway disease, care must be taken to prevent dynamic hyperinflation and the creation of auto-PEEP. Whenever possible, spontaneous breathing with CPAP or PEEP and PS is preferable. This allows patients the ability to set their own inspiratory/ expiratory ratios, and PEEP is carefully applied to match the intrinsic level of auto-PEEP the patient has generated (Smith and Marini 1988). This strategy can minimize work of breathing, and PEEP can gradually

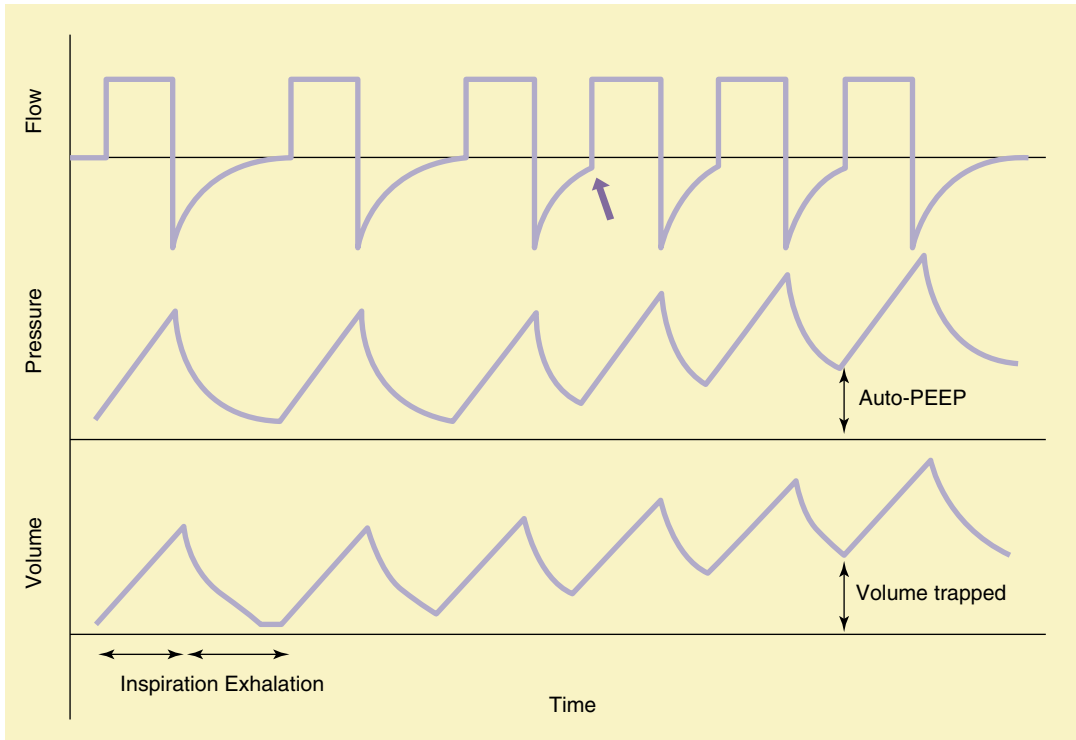


Fig. 11.52 Obstructed medium and small airways with mechanical ventilation and progressive dynamic hyperinflation from insufficient expiratory time. Note the failure of flow to return to zero during exhalation on the flow versus time graph (arrow – top). The pressure–time graph

(middle) displays progressive air trapping and generation of auto-PEEP. The volume–time graph (bottom) displays a progressive rise in lung volumes as air is trapped with each breath (Reproduced with permission, Khemani et al. (2007))

be removed as the airway obstruction improves (Wetzel 1996; Graham et al. 2007). However, if such a strategy cannot be employed and the patient is either paralyzed or heavily sedated, then care must be taken to allow sufficient expiratory time to prevent further air trapping. This can be monitored by examining the flow versus time curves, paying particular attention to expiratory flow returning to zero before the initiation of a subsequent breath. Evidence of dynamic hyperinflation may be observed on the pressure or volume versus time curves, where increased air trapping will manifest as gradual increases in end-expiratory lung volumes and pressures (Tuxen 1994; Williams et al. 1992).

If total ventilatory support is employed (no spontaneous breathing), then extrinsic PEEP may worsen air trapping. However, if the patient is completely spontaneously breathing, then the application of extrinsic PEEP to match the patient's level of intrinsic or auto-PEEP (some

advocate 80 % of auto-PEEP) will help minimize respiratory muscle fatigue. Of course, the level of support should ultimately be determined by patient comfort and work of breathing.

Large Airway Disease

A spontaneously breathing, non-intubated patient with extrathoracic obstruction (e.g., croup, laryngomalacia, tracheomalacia, vocal cord dysfunction) classically has limitation of flow during inspiration. This flow limitation manifests with a flattening of the inspiratory limb of the flow–volume loop. This can usually be overcome by bypassing the obstruction with an ETT.

If the obstruction is not bypassed by the ETT and is in the trachea distal to the tube (i.e., intrathoracic), the flow–volume loop will either show flattening on exhalation (variable lesion such as tracheomalacia) or show flattening on both inspiration and exhalation (fixed lesion) (Fig. 11.52). This latter situation is commonly seen with foreign

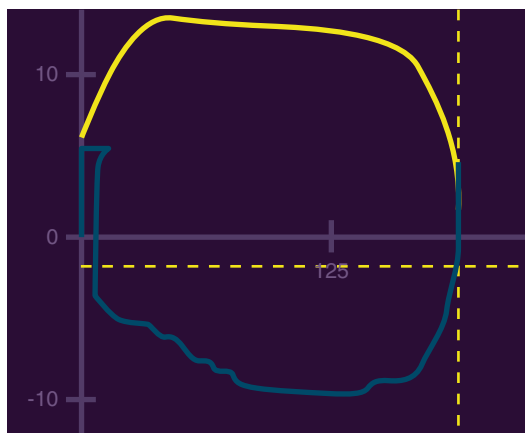


Fig. 11.53 An actual recording of a tidal breathing flow–volume loop of an intubated child with a fixed tracheal stenosis below the tip of the endotracheal tube. There is flattening of both inspiratory and expiratory limbs of the FV loop

body aspiration, tracheal stenosis, or accidental kinking of an ETT (Fig. 11.53).

Conclusion

A firm understanding of respiratory monitoring tools is invaluable for all physicians taking care of critically ill children. It allows for titrating therapeutic interventions to the patient's disease state and if used correctly can facilitate optimal respiratory support and aid in eventual weaning to endotracheal extubation. Moreover, with close monitoring, one can often detect aberrations or changes in physiologic states before disease progression, allowing for early interventions and prevention of disease progression.

Essentials to Remember

- Measurements of pulmonary function should occur as close to the tip of the endotracheal tube as possible, especially in small children and infants.
- In intubated children, pulmonary function tests will not be accurate if there is a large leak around the endotracheal tube. The leak must be minimized.
- Flow–volume loops are particularly useful for distinguishing obstructive airway

disease and restrictive lung disease on mechanical ventilation.

- Pressure–volume loops help the clinician optimize ventilator support, particularly with respect to positive end-expiratory pressure and peak inspiratory pressure.

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Part IV

Respiratory Monitoring in the Mechanically Ventilated Patient

12.1 Monitoring Oxygenation of Ventilated Infants and Children

John Salyer

Educational Goals

- Describe a basic understanding of the oxygen transport chain.
- Understand the various technologies for oxygenation monitoring during mechanical ventilation.
- Describe the limitations associated with various monitoring technologies.

Karl Wilhelm Scheele first discovered oxygen in 1772.¹ This immense milepost in the history of science and medicine set into motion events that have led us to the present in which the delivery and monitoring of oxygen is a mainstay of critical care. It is now possible to continuously measure many key aspects of the complex movement of oxygen molecules from the atmosphere to the lungs, to the blood, to the tissues, and finally, to the cellular structures that use oxygen and nutrients to create the energy molecules that fuel our biological engines. This chapter will focus on the most commonly used oxygenation monitoring techniques including their measurement principles, utility, and limitations. However, before we explore a brief review of what *can* be monitored, it is useful to consider what *should* be monitored. Sometimes, our technology develops at a pace that far exceeds our wisdom in how to use it. “New technologies and procedures have developed so rapidly—and there are such economic and social incentives to use them—that the evaluation of their safety, efficacy, and cost-effectiveness as well as the consideration of their social and ethical consequences have lagged far behind” (Mosteller and Institute of Medicine 1985). Another term for this is technology creep,

¹Although still debated, evidence suggests that Scheele discovered oxygen independently and earlier than Joseph Priestly who has been widely credited with this breakthrough because he published his findings prior to Scheele. Others have suggested that oxygen was discovered even earlier by a Michał Sędziwój, a Polish alchemist and natural philosopher in the late sixteenth century.

which refers to the continuing addition of technology that is both qualitatively and quantitatively more complex. Moreover, this often happens without any rigorous testing of the effect of this technology on patient outcomes. Most new instrument/device testing mandated by regulatory agencies prior to approval is focused on ensuring patient safety and measurement accuracy and precision, as opposed to proving that the device in question will alter patient outcomes or improve processes of care.²

Some clinicians have adopted a “more is better” philosophy, wanting to monitor nearly everything possible (Hess 1998). Excessive numbers of monitors at the bedside can produce so much information for clinicians to process that the sheer volume can outpace their ability to analyze and integrate this information into timely decision making (East et al. 1991; Graham and Cvach 2010). There can be up to 40 different monitoring alarms assaulting the intensive care clinician (Chambrin 2001). It is reported that only 15 % of all monitor alarms in an intensive care environment are clinically relevant (Siebig et al. 2010).

Add this complexity to the fact that clinicians are often not adequately trained to understand the physiology and measurement principles related to the monitors they are using. In a survey of more than 4,300 responders, 70 % of neonatal care providers acknowledged that they do not have a complete education in oxygenation and have insufficient knowledge of basic concepts (Sola et al. 2008). In the same survey, 92 % did not know how SpO₂ monitors work and the differences between various brands of SpO₂ monitors. Knowledge (or the lack thereof) about pulse oximetry has been tested among pediatric clinicians, and the results have mostly been

disappointing (Teoh et al. 2003; Popovich et al. 2004; Elliott et al. 2006).

To better understand the way in which oxygenation is monitored, the clinician must first understand the basic physiology of oxygen transport in the blood. In healthy humans, every 100 mL of arterial blood carries about 20 mL of oxygen at sea level. At rest, the body extracts about 5 mL of oxygen per 100 mL of arterial blood. This reserve allows for adequate tissue oxygenation during periods of high oxygen demand (i.e., exercise) or periods of low oxygen delivery (i.e., pulmonary and/or cardiac disease, or high altitude).

Entering the arterial blood in gaseous form, oxygen diffuses across the alveolar capillary membrane and dissolves into the plasma. But the oxygen carrying capacity of plasma alone is insufficient to sustain life. In 100 mL of plasma (with no hemoglobin), at a partial pressure of oxygen of 100 mmHg, there is only 0.3 mL of dissolved oxygen. Once dissolved in the plasma, oxygen quickly binds with hemoglobin molecules on the erythrocytes. The remarkable stereochemical properties of the hemoglobin molecule render it capable of binding to, carrying, and off-loading much more oxygen than can be dissolved in plasma alone. Once the erythrocytes have been transported through the arterial system to the capillary beds, the oxygen off-loads from the hemoglobin back into the plasma and thus diffuses across the capillary membranes into the adjacent tissues and finally through the cell membrane and into the mitochondria. Figure 12.1 visually describes some of the complex mechanisms involved in oxygen transport from the atmosphere to the tissues.

The movement of oxygen molecules through our biological systems is governed by pressure gradients. The atmosphere has a higher partial pressure of oxygen than the plasma, which is higher than the interstitial partial pressure and so on. This is illustrated in Fig. 12.2. Oxygen transport to the cells depends on the partial pressure of oxygen in the alveoli, the amount of hemoglobin in the blood, the degree to which the hemoglobin is saturated, and the cardiac output. There can also be regional variations in blood flow that can

²Not long ago, I stood at the doorway of a room in our cardiac intensive care unit watching the care of a post-operative cardiac surgery patient who was on extracorporeal membrane oxygenation. I counted 21 different LCD displays in the immediate bedside area. These included cardiorespiratory monitors, infusion pumps, oxygen monitors, ventilation monitors, and the ECMO system. And of course, each of these was connected to the tiny patient by tubing, cables, lines, and sensors. It is a tribute to the focus and dedication of the clinical staff that there are no more mishaps in this complex visual environment.

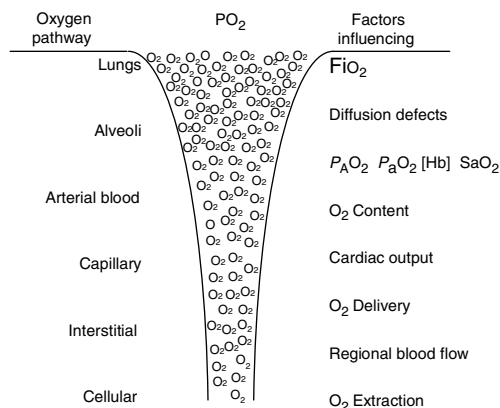


Fig. 12.1 Visual representation of the oxygen movement of oxygen from the atmosphere to the cellular level. *CO* cardiac output, *SVR* systemic vascular resistance (Used with permission from Sola et al. (2008))

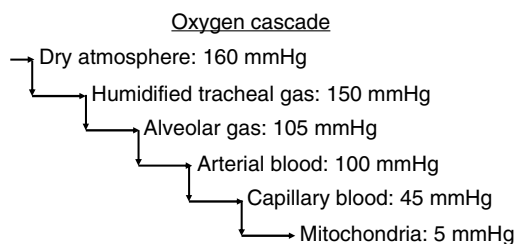


Fig. 12.2 The oxygen cascade is a conceptual rendering of the movement of oxygen from the atmosphere to the mitochondria down a descending pressure gradient. The partial pressure of oxygen in various parts of the oxygen transport chain is displayed. Various types of oxygenation monitoring systems monitor different parts of this cascade either directly or indirectly

affect oxygen transport. Finally, the diffusion of oxygen out of the plasma across the capillary membranes, into the interstitial space, into the cell, and finally into the mitochondria can be affected by interstitial fluid balances, capillary permeability, and anything else that increases the distance oxygen has to travel from the capillary wall to the adjacent cells.

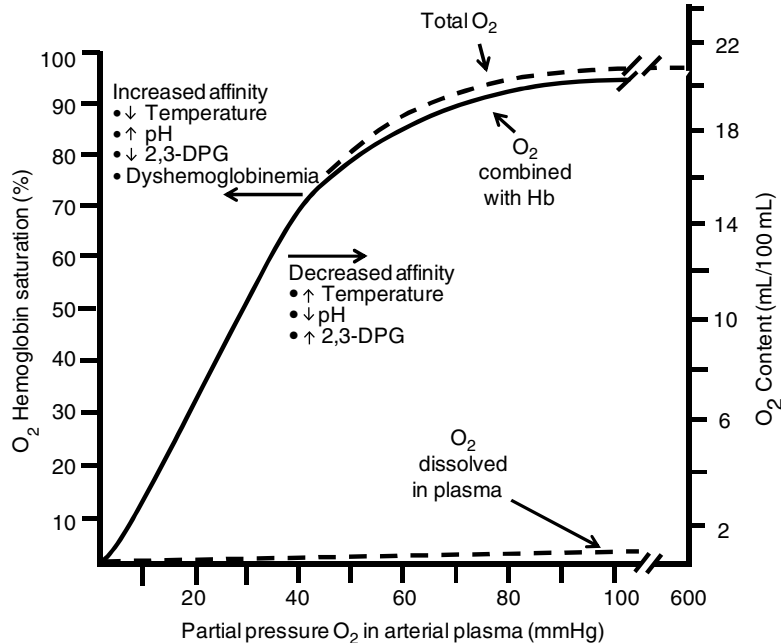
Blood gas studies assess oxygenation by measuring the partial pressure of oxygen dissolved in the plasma alone (PO_2). But this is only a small part of the oxygen transport chain. The utility of blood gas measurements are based on assumptions about the relationship between the partial pressure of dissolved oxygen in plasma and the

amount of oxygen bound to hemoglobin. This relationship is described by oxyhemoglobin dissociation curve (Fig. 12.3). The curve is sigmoid shaped to facilitate that loading of oxygen onto hemoglobin in the lungs and off-loading oxygen from the hemoglobin in the somatic capillaries. Many factors affect the shape and position of the dissociation curve. These include temperature, pH, chronic hypoxemia, dyshemoglobinemias, and the availability of 2,3 diphosphoglycerate (2,3-DPG), a compound that affects the affinity of oxygen for hemoglobin (Hsia 1998). Decreased levels of 2,3-DPG are found in cases of erythrocytosis and nonspherocytic hemolytic anemia and 2,3-DPG phosphatase deficiencies. The effect of transfusion of stored RBCs on oxygen delivery is complex, and views about its effect are divergent. Historically, it was reported that 2,3-DPG levels were depleted in stored RBCs, but others have found no relationship between the length of time of storage of RBCs and biochemical markers of oxygenation in the critically ill (Tinmouth et al. 2006; Ibrahim et al. 2005a; Walsh et al. 2004). Increased levels of 2,3-DPG are found in conditions in which the body needs more oxygen, such as obstructive lung disease, cystic fibrosis, congenital heart disease, and hyperthyroidism. High altitudes and participating in exercise sessions can also elevate 2,3-DPG levels.

In general, those factors that shift the curve to the right are advantageous to the patient since this reflects a reduced affinity of oxygen for hemoglobin resulting in more oxygen released from hemoglobin to the tissues (Peter et al. 1991). The position of the curve is usually expressed by measurement of $P50$, which is defined as the PaO_2 at which the hemoglobin is 50 % saturated with oxygen at a pH of 7.40, $PaCO_2$ of 40 mmHg, and temperature of 37 °C.

It has been known for many years that there is large variation in affinity of oxygen for hemoglobin and thus the shape and position of the dissociation curve (Gøthgen et al. 1990; Wilkinson et al. 1980). No less than Ole Siggaard-Andersen, one of the principle developers of blood gas technology has said (Gøthgen et al. 1990), "...it is essential to know the actual position of the hemoglobin-oxygen dissociation curve, as well

Fig. 12.3 Oxyhemoglobin dissociation curve. Note that the overwhelming majority of the total oxygen content is carried as oxygen bound to hemoglobin. The curve will shift left or right as affinity of oxygen for hemoglobin increases or decreases. Changes in temperature, pH, and levels of 2,3-diphosphoglycerate cause the affinity of oxygen for hemoglobin to change. Increased affinity is associated with decreased availability of oxygen to tissues (Brashers 2002). Recent work has called into question some of the assumptions about the relationship between pH and 2,3-DPG (Ibrahim et al. 2005b)



as the hemoglobin concentration in the individual patient, for correct interpretation of PO₂..... in arterial blood.” Yet, historically, we have relied heavily on P_aO₂ alone for assessing oxygenation. Unfortunately, the actual measurement of p50 is not widely available and requires the tonometry of blood. There are calculators for P50, but these are based on assumptions about oxygen hemoglobin affinity which can vary widely (Gøthgen et al. 1990).

As clinical practice has evolved, the focus on P_aO₂ as the most widely used measure of oxygenation has been enhanced by the appreciation that SaO₂ is a broader assessment of the oxygen transport chain. This value assesses a much larger portion of the mechanism of oxygen transport. It is also clear that a thorough assessment of oxygenation cannot be made without knowing the total serum hemoglobin. This can be seen when one considers the equations for oxygen content and oxygen delivery. These equations describe the volume of oxygen in a given amount of whole and the volume delivered (or available) to the tissues by the cardiovascular system:

Oxygen content (the volume of oxygen (in mL) carried in 100 mL of whole blood):

$$CaO_2 = (Hb \times 1.34 \times SaO_2) + (P_aO_2 \times 0.0031)$$

- where
- CaO₂ oxygen content of arterial blood, expressed as mL/dL (normal values are 16–22 mL/dL)
 - Hb total serum hemoglobin in g/dL
 - 1.34 the volume of oxygen (in mL) that can be carried by a gram of hemoglobin that is fully saturated with oxygen
 - SaO₂ the degree to which the hemoglobin is saturated in percent which should be expressed as a decimal for the mathematics of the formula
 - P_aO₂ partial pressure of oxygen in arterial blood in mmHg
 - 0.0031 the oxygen solubility coefficient in plasma (the number represents the mL of oxygen that will be dissolved in plasma for each mmHg of partial pressure of oxygen dissolved in plasma)

Table 12.1 Measures and derivatives of oxygenation

Measures		Normal range
Partial pressure of arterial oxygen (P_aO_2)		80–100 mmHg
Partial pressure of arterial CO_2 (P_aCO_2)		35–45 mmHg
Arterial oxygen saturation (SaO_2)		95–100 %
Mixed venous saturation (SvO_2)		60–80 %
Arterial oxygen content (CaO_2)	$(Hb \times 1.34 \times SaO_2) + (0.0031 \times P_aO_2)$	17–20 mL/dL
Venous oxygen content (CvO_2)	$(Hb \times 1.34 \times SvO_2) + (0.0031 \times PvO_2)$	12–15 mL/dL
A–V oxygen content difference ($C[a-v]O_2$)	$CaO_2 - CvO_2$	4–6 mL/dL
Oxygen delivery (DO_2)	$CaO_2 \times CO \times 10$	950–1,150 mL/min
Oxygen delivery index (DO_2I)	$CaO_2 \times CI \times 10$	500–600 mL/min/m ²
Oxygen consumption (VO_2)	$(C(a-v)O_2) \times CO \times 10$	200–250 mL/min
Oxygen consumption index (VO_2I)	$(C(a-v)O_2) \times CI \times 10$	120–160 mL/min/m ²
Oxygen extraction ration (O_2ER)	$[(CaO_2 - CvO_2)/CaO_2] \times 100$	22–30 %
Oxygen extraction index (O_2EI)	$[SaO_2 - SvO_2]/SaO_2 \times 100$	20–25 %

Oxygen delivery:

$$DO_2 = CaO_2 \times CO \times 10$$

where

DO_2 oxygen delivery expressed as mL/min

CaO_2 oxygen content of arterial blood expressed as mL/dL

CO cardiac output expressed in mL/min

These formulae and other measures and derivatives of oxygenation, and their normal values are listed in Table 12.1. Careful review of these formulae reminds us that oxygen delivery is dependent on many factors including serum hemoglobin levels, cardiac output, oxygen saturation, and P_aO_2 .

12.1.1 Effects of Altitude

As altitude increases, barometric pressure decreases. Thus, even though the concentration of oxygen in the atmosphere is the same regardless of altitude, the partial pressure of oxygen decreases at increasing heights above sea level (Gallagher and Hackett 2004). As the P_aO_2 decreases, so does the SaO_2 . Figure 12.4 demonstrates the effect of altitude on the pressure of inspired oxygen (P_iO_2), P_aO_2 , and SaO_2 (Hackett et al. 2001).

The effect of altitude on “normal” pulse oximetry readings in infants and children has been studied (Beebe et al. 1994; Niermeyer et al. 1993, 1995; Thilo et al. 1991; Gamponia et al. 1998). Thilo reported that at an altitude of 1,610 m, healthy newborns had a mean SpO_2 of 92–93 % and that the lower end of the reference range was as low as 86 % during quiet sleep at 1–3 months of age (Thilo et al. 1991). Niermeyer et al. studied serial SpO_2 at an altitude of 3,100 m, measured from birth to 4 months in healthy infants. SpO_2 ranged from 80.6 ± 5.3 to 91.1 ± 1.7 % during the 4 months period (Niermeyer et al. 1993).

The clinician is challenged with knowing how low SpO_2 must go before supplemental oxygen is indicated at various altitudes. Subhi and colleagues did a systematic review of published normal SpO_2 for children at various altitudes above sea level (Subhi et al. 2009). Tables 12.2 and 12.3 and Fig. 12.4 are adapted from their work. Figures 12.4 and 12.5 offers threshold values below which a child may be considered hypoxemic adjusted for altitude and thus requiring supplemental oxygen. The risk of the development of retinopathy of prematurity in low-birth-weight infants requires that different target values for SpO_2 be used. See the section below on pulse oximetry.

Table 12.2 Normal (reference) ranges for blood gases in neonatal and pediatric populations

Age range	Neonatal			Pediatric	
Source	Arterial	Venous	Capillary (Cousineau et al. 2005)	Arterial	Venous
pH	7.35–7.45	7.31–7.41	7.31–7.47	7.35–7.45	7.31–7.41
PCO ₂	35–45 mmHg	41–51 mmHg	29–49 mmHg	35–45 mmHg	41–51 mmHg
PO ₂	50–90 mmHg	30–40 mmHg	33–61 mmHg	80–100 mmHg	30–40 mmHg

Table 12.3 Normal pulse oximetry values for children 1–5 years of age at various altitudes

Age of study group	Number of children studied	Altitude above sea level (m)	Reported SpO ₂ mean (SD)
2–60 months	153	3,750	88.9 (2.9)
2–23 months	80	1,500	98.9 (1.0)
0–2 months	302	1,584	97.1 (2.7)
1–60 months	151	1,600	95.7 (2.7)
1 month	100	1,610	93.4 (2.0)
7 days–36 months	87	1,670	95.7 (1.6)
0–24 months	189	2,640	93.3 (2.1)
0–18 months	55	2,600	93.2 (3.0)
0–60 months	150	2,800	92.0 (2.0)
2 days–22 months	72	2,800	91.7 (2.1)
0–60 months	152	4,018	87.8 (3.8)

Adapted with permission from Subhi et al. (2009)

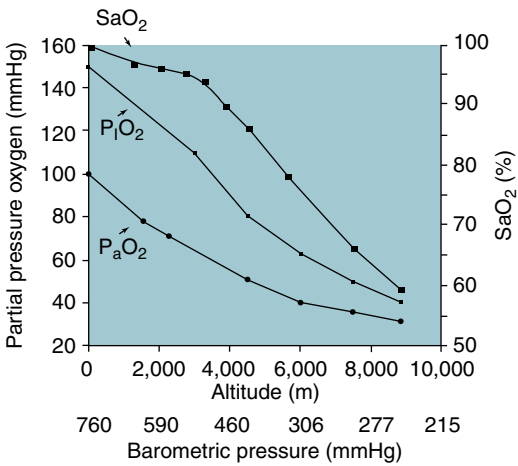


Fig. 12.4 Relationship between altitude, barometric pressure, pressure of inspired oxygen ($P_I O_2$), $P_a O_2$, and SaO_2 (Adapted with permission from Hackett et al. (2001))

12.1.2 Blood Gas Measurements

12.1.2.1 Intermittent

Intermittent sampling and analyses of the pH, PCO₂, and PO₂ of arterial, venous, or capillary blood are some of the most frequently ordered

laboratory tests. There have been tremendous advances in blood gas technology including miniaturization of components, improved quality control, simplified maintenance techniques, reduced sample size, decreased throughput time, and portability. But the measurement principles for blood gases remain the same. Blood gas machines actually measure only three variables, pH, PCO₂, and PO₂. All other variables reported on a blood gas, i.e., base excess, bicarbonate, and oxygen saturation,³ are calculated.

Blood gas machines use electrochemical sensors which are covered with selectively permeable membranes that allow the passage of either O₂ or CO₂. These gases then chemically react with reagents in their respective sensors to create voltages that are proportional to the amount of the respective gas that has entered the electrode, which correlates with the partial pressure of gas in the blood that has come in contact with the semipermeable membranes.

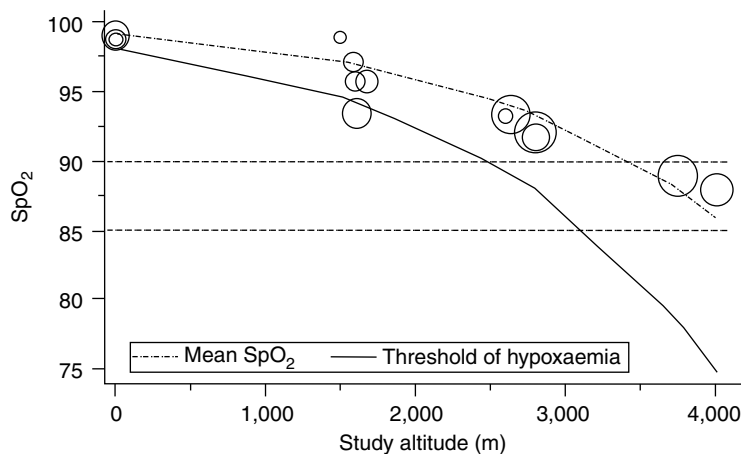
Advantages of intermittent blood gas sampling include well-known accuracy and precision, simplicity, convenience, relatively low cost, and a generally good understanding of the basics of blood gas measurement. Typically, PO₂ electrodes are less accurate and precise than PCO₂ electrodes. Intra-instrument imprecision⁴ is much improved in newer models of blood gas analyzers. For PO₂ samples <150 mmHg, most instruments can produce measurements within $\pm 2\%$ (Hansen et al. 1989; Scuderi et al. 1993). This imprecision worsens in PO₂ > 150 mmHg.

Disadvantages include the need for an invasive blood sample, either through repeated

³Later in this chapter, the limitations of the calculation of oxygen saturation are discussed in detail.

⁴Intra-instrument imprecision can be thought of as the variability of repeated samples of the same blood run consecutively in the same instrument.

Fig. 12.5 Estimated threshold of hypoxemia at different altitudes. Study estimates are plotted as circles, with size proportional to the precision of the transformed study estimate (Used with permission from Subhi et al. (2009))



percutaneous arterial or capillary sticks. Patients on ventilators for many days, can have much bruising and skin injury from repeated sticks, which can be very disturbing to parents, even though they typically heal without difficulty. Arterial lines obviate the need for repeated sticks, but in infants and children, utilization of arterial lines is not as prevalent as in adults. This is probably related to many factors including the pain of insertion, the limitations of the size of the patients, the risk of infection and mishap, and the known sequela of arterial lines.

From the early days when 10 mL of blood and 45 min was required to obtain and analyze a sample, we now have instrumentation that allows for blood gas measurements on far less than 1 mL of blood with results available within 90 s using handheld point of care analyzers. Whether or not having all blood gas results this rapidly ultimately affects patient outcomes remains largely unproven (Giuliano and Grant 2002).

Kendall and colleagues (1998) randomized 1,728 patients to be managed in the emergency room using either point of care or central laboratory testing. They found that point of care testing (which included blood gas, hematological, and chemical studies) reduced the time until lab results were available (for blood gases, a 20 min reduction). But they deemed that change in management in which timing was critical involved only 7 % of all samples. Moreover, there was no difference between groups in hospital admission rate, length of stay in the emergency department, hospital length of stay, and mortality.

In a very interesting study, Thomas and colleagues (2009) compared P_aO_2 and P_aCO_2 values from a point of care testing system to values obtained from a central laboratory with regard to running a ventilator management algorithm in 446 ventilated adult intensive care patients. In other words, would the recommendations of the ventilator management algorithm be different when using point of care values or central laboratory-derived blood gases? They concluded that the use of point of care blood gases versus central blood gas laboratory values produced equivalent ventilator management algorithm recommendations. Their study included no cost analyses.

Despite increased proliferation of handheld, point of care blood gas analyzers, there remains tremendous variation in the use of these devices. Some intensive care units rely exclusively on point of care testing for blood gas analysis. Others use little or no point of care testing, relying instead on near patient, bench blood gas analyzers, or analyses done in a central laboratory.

A search has been underway for more than 10 years to prove that point of care testing is cost effective. Results have been divergent depending on what type of point of care testing is being studied (O'Connell et al. 2008; Macnab et al. 2003; Englander et al. 2006). Clearly, there are some cases where immediate testing results at the bedside seem likely to make a meaningful difference in outcomes, such as in surgery, during ECMO, or during transport. But my observations have led me to conclude that in a typical intensive

care setting, the vast majority of point of care blood gas testing is not emergent and that results within 15–30 min would be completely acceptable. Additionally, any potential savings of implementing point of care blood gases systems would be dependent on elimination of the instrumentation and labor costs of other blood gas analysis systems. Most applications of point of care blood gas testing I have seen simply layered the point of care capabilities on top of existing laboratory blood gas systems, resulting in cost increases with no proven effect on patient outcomes. Most of the published financial analyses of the impact of point of care testing are not sophisticated and often confuse the cost of the blood gases with the charges for blood gases. The interested learner is directed to a thorough review of the general topic of point of care testing by Kost (1998).

Many blood gas instruments do not actually measure SaO_2 , but instead calculate (or estimate) the SaO_2 based on assumptions about the shape of the oxygen dissociation curve. Wilkinson et al. showed that in some newborns, when $P_a\text{O}_2$ was less than 50 mmHg, calculated SaO_2 could be >90 %, whereas in others <75 % (Wilkinson et al. 1980). My colleagues and I showed that in pediatric ICU patients, calculated oxygen saturation levels were unreliable, particularly when true saturation levels were <90 % (Salzer et al. 1989). Clinicians are advised not to rely on *calculated* oxygen saturation values derived from blood gas measurements.

The most common method of direct laboratory measurement of SaO_2 requires the use of a CO-oximeter. This name can be a little misleading since it was derived from early instruments designed to measure carboxyhemoglobin (HbCO). Laboratory CO-oximeters use multiple wavelength spectrophotometry of hemolyzed blood samples to measure SaO_2 . This measurement principle is basically the same as is used in pulse oximetry, which we will discuss in detail later. Typically, point of care blood gas tests do not actually measure SaO_2 so care must be taken in interpreting low saturation values from point of care devices. Some of the latest bench blood gas analyzers incorporate spectrophotometry into

their measurement capabilities and thus can report actual measured SaO_2 . The interested clinician should check and ensure that the SaO_2 's reported with blood gas results are actually measured using CO-oximetry versus calculated.

12.1.2.2 Continuous Blood Gas Monitoring

Continuous intravascular monitoring of blood gases became widely available in the 1990s and has been steadily improving since then (Ganter and Zollinger 2003). This technology uses various techniques to miniaturize blood gas measurement sensors sufficiently to allow them to be imbedded in a catheter that can be placed in the radial, brachial, and femoral artery for continuous monitoring. Measurement principles may be electrochemical (as in bench blood gas analyzers) or photochemical/optical (also called optodes). Optodes use sample chambers that contain dyes which are illuminated with light of a certain wavelengths. The illuminating light will be transmitted, reflected, absorbed, and reemitted proportionally to the concentration of oxygen, carbon dioxide, and hydrogen ions in the sample.

The radial artery is the most common site for catheter insertion in adults and the femoral artery in children <5 years old. The disadvantages of the radial approach include increased susceptibility to motion artifact, vasospasm, and changes in peripheral blood flow. Nevertheless, this approach is chosen routinely in adults and older children, because of easy access, the double blood vessel supply of the hand, and low complication rates. For newborns, the umbilical artery is used.

Proponents of this technology argued that substantial changes in arterial blood gases can be missed by intermittent blood gas analyses (Zaugg et al. 1998). Moreover, it is suggested that continuous blood gas monitoring could (1) allow for more rapid identification of changing trends in blood gases, (2) decrease therapeutic decision time, (3) reduce blood loss from repeated sampling, and (4) make it possible to use the continuous blood gas results for closed loop control of ventilator settings using feedback-control algorithms (Mahutte 1998). As is the case with so

much new technology, little systematic investigation has been done to validate these assumptions.

These systems are very costly. The instruments themselves cost as much as a bench blood gas analyzer and yet can only be used on one patient at a time. The catheters are also very costly, and some patients end up needing more than one because of catheter failure. They are also very invasive and prone to technical problems such as kinked or clotted catheters and problems with poor regional blood flow. In my experience in the USA visiting many pediatric intensive care units, I have seen very few in use.

12.1.3 Pulse Oximetry

One of the more remarkable advances in oxygenation monitoring technology is the development of the pulse oximeter (Salzer 2003). Pulse oximeters use principles of spectrophotometry to estimate arterial oxygen saturation noninvasively using sensors that can be clipped to an ear or finger or, for smaller patients, can be wrapped around digits, palms, and feet. Pulse oximetry *estimates* arterial oxygen saturation by measuring the absorption of light of two wavelengths, approximately 660 nm (red) and 940 nm (infrared), in human tissue beds. As light passes through human tissue, it is absorbed in various degrees by the skin, tissues, bone, fluids, and blood. The amount of blood in the tissue beds changes with each beat of the heart. This change in volume causes a change in spectral absorption, which the oximeter can detect and thus estimate heart rate. As the relative amounts of oxygenated and deoxygenated hemoglobin changes in the tissue bed, the spectral absorption also changes, and thus the oximeter can estimate SaO₂.

The accuracy of pulse oximetry has been studied extensively in various populations (Choe et al. 1989; Morris et al. 1989; Faconi 1988; Hay et al. 1989; Nickerson et al. 1988; Severinghaus et al. 1989; Hannhart et al. 1991; Taylor and Whitman 1988; Wouters et al. 2002a, b; Deckardt and Steward 1984; Jennis and Peabody 1987; Walsh et al. 1987; Southall et al. 1987; Solimano et al. 1986; Ramanathan et al. 1987; Praud et al.

1989; Boxer et al. 1987; Carter et al. 2001) and is generally about $\pm 1\text{--}2\%$ of readings $>85\%$ (Severinghaus 1993; Emergency Care Research Institute 2003; Van de Louw et al. 2001). During periods of profound desaturation (typically below 70–80 %), bias and precision of oximeters deteriorates significantly, being highly variable depending on brand (Faconi 1988; Severinghaus et al. 1989). This limitation has never been particularly problematic for most clinicians since an SpO₂ of 40 % versus 60 % will illicit the same aggressive interventions to improve oxygenation.

As we have learned more and more about the behavior of oximeters during continuous monitoring, it has become apparent that there are serious performance problems with some types of pulse oximeters that are not related to accuracy, but instead to precision and reliability, e.g., the ability of the devices to produce credible readings over time. More about this are discussed below.

Continuous monitoring with a pulse oximeter was originally mostly confined to the perioperative period. But it has now grown in many places to include all intensive care patients, any child on oxygen, anyone undergoing procedural sedation, anyone presenting with respiratory symptoms in the emergency department, or anyone on patient-controlled anesthesia, to name a few. Indeed, SpO₂ readings have become a de facto fifth vital sign. In terms of processes, pulse oximetry has been shown to sometimes reduce the number of arterial blood gas samples obtained in various populations (King and Simon 1987; Kellerman et al. 1991; Inman et al. 1993; Bourdelles et al. 1998; Roizen et al. 1993; Niehoff et al. 1988).

But as the use of pulse oximetry spread, little evidence was developed demonstrating the effect of continuous monitoring with a pulse oximeter on outcomes of care. It has been said that “absence of evidence is not evidence of absence.”⁵ Many technologies have not been thoroughly tested, and thus their effect on outcomes has been suspect. But it is risky to then build arguments

⁵This quote should be interpreted to mean that having not looked for something, and thus not found it, does not necessarily mean that it is not there.

based on the assumption that this absence of evidence is a result of having looked for it and not found it. But in the case of oximetry, there has been a decade long search for proof that continuous monitoring changes the outcomes of care. For most of this time, no such effect has been found (Ochroch et al. 2006; Pedersen et al. 2009).

Moeller et al. enrolled more than 20,800 surgical patients and randomized them to receive continuous pulse oximetry during the perioperative period. The two groups did not differ significantly in cardiovascular, respiratory, or neurologic complications; length of hospital stay; or in-hospital deaths (Moller et al. 1993a).

It is possible that not using the pulse oximeter and, thereby, not identifying and treating episodic hypoxemia might have more subtle effects on the higher brain functions of memory and cognition. In a follow-up study, Moeller and colleagues studied this question by randomizing 736 surgical patients to continuous pulse oximetry during the perioperative period (Moller et al. 1993b). Cognitive function was evaluated before surgery, at 7 days and 6 weeks following surgery. The authors concluded that “. . . subjective and objective measures did not indicate less postoperative cognitive impairment after perioperative monitoring with pulse oximetry.”

Bowton et al. studied (1991) the effect of continuous pulse oximetry on a population of general medical–surgical patients. Reviews of the oximeter records were compared with the nurses’ charting, doctors’ progress notes, and doctors’ orders. Desaturations that were identified by the pulse oximeter were noted in the nursing notes only 33 % of the time and in the doctors’ progress notes 7 % of the time. Changes in the orders for respiratory therapy were noted in only 20 % of patients who desaturated to <85 %.

A Cochrane systematic review of the effect of pulse oximetry in the perioperative period by Pedersen et al. (2009) concluded, “. . . studies confirmed that pulse oximetry can detect hypoxaemia and related events. However, we have found no evidence that pulse oximetry affects the outcome of anaesthesia for patients. The conflicting subjective and objective results of the studies, despite an intense methodical collection of data

from a relatively large general surgery population, indicate that the value of perioperative monitoring with pulse oximetry is questionable in relation to improved reliable outcomes, effectiveness, and efficiency. Routine continuous pulse oximetry monitoring did not reduce either transfer to ICU or mortality, and it is unclear if there is any real benefit from the application of this technology in patients who are recovering from cardiothoracic surgery in a general care area.”

However, both my observations of how oximeters are actually used and a careful reading of the literature lead me to conclude two important things about the impact of continuous pulse oximetry on patient outcomes. First, not all oximeters perform the same, and second, an oximeter will not substantially alter patient care unless it is used by people who are thoroughly trained and in conjunction with a systematic methodology for how to set oximeter alarms and how to react to oximeter alarms. We know that clinicians are generally not very well trained in exactly what a pulse oximeter measures, and they know very little about performance differences between brands (Sola et al. 2008; Teoh et al. 2003; Popovich et al. 2004). And collectively, we are beginning to understand that superimposing additional technology on top of unreliable clinical processes will not necessarily improve the process at all, but may instead simply create a more technologically advanced unreliable process (Stapleton et al. 2009; Thompson et al. 2003).

Anyone who has long worked in the quality assurance field of health care will appreciate that policy and practice may often not be well acquainted. In the case of pulse oximeter alarm limits, this is particularly true. It has been shown that compliance with pulse oximetry alarm limit policies is as low as 9 % of patients (Clucas et al. 2007). This has certainly been my clinical experience. This is probably largely due to the propensity of some brands of pulse oximeters to generate lots of false desaturations. The clinicians are simply setting the alarm limits at levels that will keep the oximeters from driving them to distraction. Even so, there is still a great deal of alarm desensitization because of the poor performance of some brands of pulse oximeters. This noncompli-

ance is also probably a contributing factor in why it was originally difficult to show an influence of pulse oximetry on patient outcomes. But as technology and clinical processes have improved and standardized, the impact of pulse oximetry has become more detectable.

As an example, Durbin and Rostow demonstrated that using motion-resistant⁶ pulse oximetry technology in conjunction with a standardized process of postoperative weaning resulted in a reduction in oximeter failure rates, arterial blood gas utilization, and oxygen weaning time in adult cardiovascular surgery patients when compared to a conventional pulse oximeter (Durbin and Rostow 2002).

Chow et al. also demonstrated improved outcomes associated with the implementation of an oxygen management protocol while switching to motion-resistant pulse oximetry (Chow et al. 2003). In this study of low-birth-weight infants, retinopathy of prematurity rates went from 12.5 to 2.5 % after introduction of new pulse oximeter technology and a rigorous oxygen management protocol.

Taenzer et al. reported that unplanned transfers to the intensive care unit decreased by 48 % after introduction of motion-resistant pulse oximetry and a centralized monitoring system⁷ to an orthopedic unit (Taenzer et al. 2010). This system sends all pulse oximetry data via wireless technology to a central computer server that notifies nurses by pager when their patients desaturated.

12.1.3.1 Limitations of Pulse Oximetry

Not all pulse oximeters are created equal. Although the accuracy of pulse oximeters has been demonstrated repeatedly, there are serious issues with the ongoing precision and reliability of the readings produced. Most studies of oximetry performance have focused on comparing single SpO₂ readings to the SaO₂ of simultaneously drawn arterial blood samples that are measured in a CO-oximeter. When this is done, accuracy is typically ± 2 %

(actual reading). The more important issue for monitoring critically ill patients is the reliability of continuous readings over time. False alarms can be a major problem in critical care units (Lawless 1994; Bohnhorst and Poets 1998). It turns out that in neonatal, pediatric, and adult populations, some pulse oximetry technology is prone to increased false desaturation readings and data dropout, which is defined as the amount of time the pulse oximeters display no reading at all.

In infants and children, the most common limitation is the effect of motion and low perfusion (Pettersen et al. 2007). As children move the extremity being monitored, wiggling their fingers and toes, or experience periods of low perfusion, the absorption being measured by the oximeter is constantly changing in an environment where the signal-to-noise ratio of the changes in absorption is very low. These changes can be misinterpreted by oximeters as false desaturations or even cause some oximeters to display no readings at all (data dropout). Some pulse oximeters use sophisticated signal processing algorithms to filter and analyze these signals and determine through statistical modeling if the readings are reliable enough to be displayed. This is typically called motion resistance, and it is claimed by a number of manufacturers (Bohnhorst and Poets 1998). The computer in the oximeter must decide if the data at hand should be displayed, and the complex confidence arbitration algorithms for this are proprietary and thus the exact details of how this is done are often not available. How well these various algorithms work is a point of great debate among manufacturers.

The clinicians must also be aware that pulse oximetry software is frequently changing, and although your hospital may have only one brand of oximetry, you may have many different software versions that perform differently. Another confounder when thinking about pulse oximeter performance is the misleading use of one manufacturer's sensors by another manufacturer. As an example, if you buy Philips multiparameter monitoring systems, you can get many different software and hardware configurations. You can get their monitors equipped with Nellcor, Masimo, or Philips oximetry signal processing software.

⁶ Motion-resistant pulse oximetry will be discussed in detail in a later section of this chapter.

⁷ Both the oximetry and the monitoring system were manufactured by Masimo Inc, Irvine CA, USA.

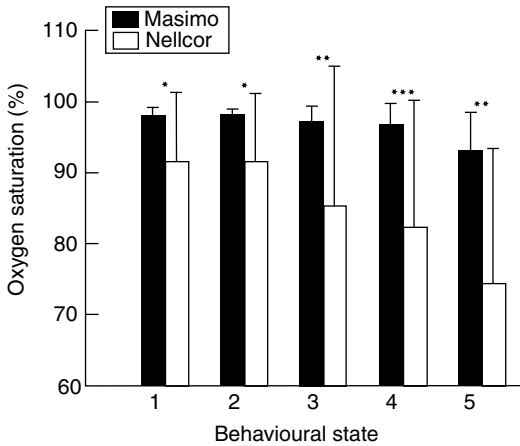


Fig. 12.6 Oxygen saturation measurements (means (SD)) with Masimo and Nellcor pulse oximeters in 15 healthy infants during different behavioral activity states: 1 quiet sleep, 2 indeterminate sleep, 3 active sleep, 4 awake, 5 crying. * p , 0.02; ** p , 0.005; *** p , 0.0005 (Used with permission from Sahni et al. (2003))

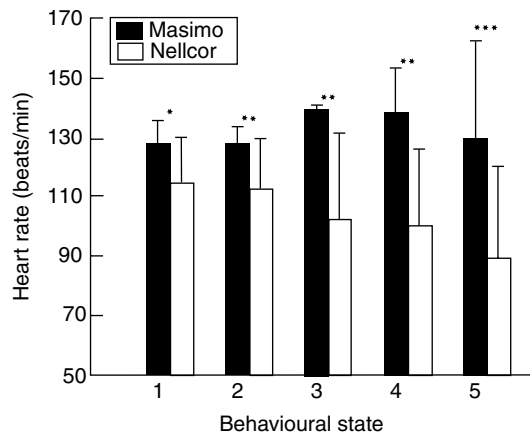


Fig. 12.7 Heart rate measurement (means (SD)) with Masimo and Nellcor pulse oximeters in 15 healthy infants during different behavioral activity states: 1 quiet sleep, 2 indeterminate sleep, 3 active sleep, 4 awake, 5 crying. * p , 0.005; ** p , 0.0005; *** p , 0.00005 (Used with permission from Sahni et al. (2003))

You can also use Nellcor probes with Philips signal processing. Thus, clinicians may look at the Nellcor sensor and assume they have Nellcor signal processing in their multiparameter, which they may not. Sometimes, the front-line manufacturer representatives are not forthcoming with this information.

Ahlborn et al. (2000) showed that the use of the motion-resistant pulse oximetry of Masimo Signal Extraction Technology (SET)⁸ in a population of low-birth-weight infants resulted in a 75 and 47 % reduction in false alarm rates compared to two other brands of oximeters.

Sahni and colleagues (2003) studied a population of 15 healthy infants during various activity states. They showed that the use of Masimo SET resulted significantly less artifact. Figures 12.6 and 12.7 show SpO₂ and heart rate readings from the two brands of oximeters in these healthy infants during various activity states.

In another study which compared neonatal transcutaneous PO₂ (T_cPO₂) measurements to SpO₂, Bohnhorst and colleagues showed that episodes of hyperoxia detected by T_cPO₂ were missed by the Masimo SET technology in only 0.5 % of episodes compared to 5.4 % by another brand (Bohnhorst et al. 2000).

Table 12.4 Incidence of performance problems of four new-generation pulse oximeters in a neonatal population

	Masimo SET	Nellcor N-395	Novametrix MARS	Philips Viridia
False hypoxemia	1	42	35	10
Data drop outs	1	10	95	21

Used with permission from Hay et al. (2002)

In another study of the utility of various brands of pulse oximeters in neonates, Hay and colleagues (2002) showed that there were 86 % fewer false hypoxemias with the Masimo SET than other brands. Table 12.4 shows the results of this study for four different brands of oximeters. Data drop-outs have also been shown to be much lower with the Masimo SET technology compared to some brands of oximeters (Workie et al. 2005).

Torres et al. compared Masimo SET technology to another brand in postoperative pediatric cardiopulmonary bypass patients and reported that the SpO₂ failure rates were 10 % in the Masimo and 41 % in the other brand (Torres et al. 2004).

Another important limitation of pulse oximeters is presence of elevated levels of dyshemoglobins such as carboxyhemoglobin, methemoglobin, and sulfhemoglobin. These variants of hemoglobin arise out of various clinical conditions such

⁸Masimo Inc. Irvine California, USA.

Table 12.5 Pulse oximetry readings, P_aO_2 , actual arterial saturation, and methemoglobin (MetHb) levels in a 12-month-old infant suffering from phenazopyridine hydrochloride ingestion

Time	P_aO_2 (mmHg)	SpO ₂ (%)	SaO ₂ (%)	MetHb (g/dL)
Admission	155	63	44	55
4 h	102	81	66	30
16 h	110	89	82	15
24 h	100	95	93	6

Used with permission from Watcha et al. (1989)

as carbon monoxide inhalation, nitric oxide therapy, and the ingestion of certain poisons. These dyshemoglobins cannot bind adequately with oxygen and when elevated can cause a patient to have a very low true oxyhemoglobin desaturation in the presence of very high P_aO_2 's. Thus, relying on P_aO_2 alone, the clinician may have a false sense of security regarding the patient's level of saturation. Table 12.5 demonstrates this phenomenon in a 12-month-old child. Nearly all currently available pulse oximeters cannot distinguish oxyhemoglobin from these dyshemoglobins and thus will read falsely high in the presence of elevated levels. To measure these, an oximeter would have used more than two wavelengths of light (as does a CO-oximeter). Masimo has marketed a pulse oximeter that purports to measure total serum hemoglobin, carboxyhemoglobin, and methemoglobin noninvasively. Little controlled scientific data has yet been subjected to peer review on this product. Early reports are promising (Annabi and Barker 2009; Barker et al. 2006; Rabe et al. 2010) but the technology needs to be subjected to more testing under more challenging conditions in various populations.

12.1.4 Summary

The movement of oxygen through the human body is a complex phenomenon. It is important for the clinicians to understand which part of the oxygen transport chain is being measured by various oxygenation monitoring technologies. Heavy reliance on P_aO_2 measurements alone may give a limited view of oxygenation monitoring. Other factors to consider are cardiac output, serum hemoglobin levels, and the oxygen saturation of

hemoglobin. Normal oxygen saturation diminishes with increasing altitude.

Point of care blood gas testing has gained widespread acceptance without any compelling evidence that it has substantially altered patient outcomes.

Pulse oximetry has greatly simplified oxygenation monitoring and can be a powerful and convenient tool for oxygenation monitoring. However, there continue to be knowledge deficits of the clinicians regarding what oximeters actually measure and how the performance of oximeters vary between and within brands. While pulse oximetry accuracy has been well established, there are significant problems with the reliability of readings over time with some brands. Motion-resistant pulse oximetry (Masimo SET) has been shown to significantly reduce false desaturations and data dropout when compared to other pulse oximeters.

Essentials to Remember

- The movement of oxygen through the human body is complex.
- The most common measures of oxygenation, P_aO_2 , and SaO₂ only measure certain aspects of the oxygen transport system. A more thorough understanding of the oxygen transport system and oxygenation monitoring technology will help clinicians make decisions based on the data from continuous or intermittent oxygenation monitoring.
- Point of care invasive oxygenation studies like blood gases have not been shown to substantially alter the outcomes of care when compared with centralized laboratory testing.
- The most widely used measure of oxygenation is pulse oximetry.
- There are important performance differences between brands of oximeters.
- Motion-resistant oximeters are superior and reduce false desaturations, false alarms, and data dropout. When used with carefully controlled clinical protocols, they can also alter care processes and improve patient outcomes.

12.2 Ventilation: Adequacy of Breathing Assessment

Gerd Schmalisch, Ira M. Cheifetz

Educational Aims

- Understand the differences between time-based and volume-based (volumetric) capnography.
- Review technologic considerations of capnography.
- Understand the interpretation of the various phases of the time-based capnogram.
- Discuss the unique aspects of carbon dioxide monitoring in the premature infant population.
- Understand the interpretation of the phases of the single-breath carbon dioxide waveform associated with volumetric capnography.
- Review the effects of both ventilation and perfusion on carbon dioxide elimination.
- Discuss the various clinical applications of time-based and volume-based capnography.
- Review the prognostic value of the dead space to tidal volume ratio (V_d/V_t).

12.2.1 Capnography

Noninvasive carbon dioxide monitoring provides valuable clinical information for the neonatal, pediatric, and adult patient populations. Capnography is an essential monitoring system for critically ill patients and is increasingly being described as the fifth vital sign.

Capnometry is the digital display of data, while capnography is the graphical display of data which can be presented time based or volume based (i.e., volumetric; see Sect. 12.2.3). Capnography refers to the visual depiction via waveforms of exhaled CO_2 during the entire respiratory cycle and is a better indicator for dynamic changes in a patient's gas exchange than capnometry. When capnography is used, proper

clinical interpretation of the data and waveforms is essential to provide optimal management of the ventilator as well as safe patient care.

Time-based capnography is commonly known as end-tidal carbon dioxide (etCO_2) monitoring. A time-based capnogram provides qualitative information on the waveform patterns associated with invasive ventilation and a quantitative estimation of the partial pressure of expired CO_2 . Volumetric capnography utilizes a CO_2 sensor and a pneumotachometer in combination. This approach permits the calculation of the net volume of CO_2 expired and is expressed as a volume exhaled per unit time (most commonly mL/min) rather than a partial pressure or gas fraction. Additionally, volumetric capnography allows for the calculation of the airway dead spaces, including the dead space to tidal volume ratio (V_d/V_t).

12.2.2 Time-Based Capnography/End-Tidal Carbon Dioxide Measurements

12.2.2.1 Methods, Waveforms, and Nomenclature

End-tidal carbon dioxide measurement is one of the primary variables obtained from time-based capnography. For these measurements, the required interface with the ventilator circuit is called a capnograph. Carbon dioxide elimination can be measured by either mainstream or sidestream technology.

Several studies, in particular in infants, have demonstrated that mainstream measurements are superior to sidestream measurements from the technical perspective (Pascucci et al. 1989). Mainstream sensors have a faster response time, such that reliable single-breath CO_2 measurements, even at high respiratory rates, are possible. However, the additional apparatus dead space (V_{Dapp}) of the CO_2 analyzer chamber leads to rebreathing of the exhaled CO_2 , which should be considered; however, V_{Dapp} is generally only clinically significant in very small infants. Mainstream sensors have become the more typical approach for capnography in mechanically ventilated larger infants, children, and adults.

Sidestream measurements utilize a sample port at the endotracheal tube (ETT) and are void of dead space; however, the suction flow rate required to sample exhaled gas may adversely affect measurement accuracy and response time. In neonates with a minute ventilation of about 200 mL/min/kg body weight, the suction flow must be sufficiently low to prevent dilution by surrounding air that will occur when the expiratory gas flow rate falls below the suction flow rate. A microstream capnograph using a suction flow of 30 mL/min and a miniaturized sample chamber has been developed, thus, improving the measurement accuracy for intubated infants (Hagerty et al. 2002; Kugelman et al. 2008).

Several techniques to measure the CO₂ in expired air have been developed (Gravenstein et al. 2004). Currently, infrared (IR) spectrography and mass spectrometry (mainly for multiple gas analyses) are most frequently used. However, only IR spectrography utilizes miniaturized, low-cost main- and sidestream sensors optimized for measurements in the infant population. An alternative fast method could be the molar mass measurement of the breathing gas by ultrasound spirometry. Of note, ultrasonic flow meters have a very short response time without a time delay between the measured air flow and molar mass of the breathing gas. Theoretically, such devices are well suited for volumetric capnography in small lungs. However, molar mass techniques utilize a surrogate signal which is influenced by all components of the expired gas, and, thus, it is difficult to separate the CO₂ signal (Thamrin et al. 2007).

Capnographs measure either the partial pressure (PCO₂) (IR analyzer) or the CO₂ fraction (FCO₂) of the breathing gas (mass spectrometers). The relationship is given by Dalton's law:

$$PCO_2 = (P_B - 47 \text{ mmHg}) \cdot FCO_2 \quad (12.1)$$

where P_B is the barometric pressure and 47 mmHg is the water vapor pressure at 37 °C. However, with a dry gas (e.g., calibration gas from a gas cylinder), PCO₂ is calculated by:

$$PCO_2 = P_B \cdot FCO_2 \quad (12.2)$$

The time-based waveform of the measured PCO₂ (or FCO₂) is called a capnogram and can be divided into four phases as shown in Fig. 12.8. Phase I starts with inspiration and represents, after a short CO₂ rebreathing, mainly the CO₂-free inspired gas. Phase II starts with exhalation and consists of a rapid S-shaped upswing on the tracing due to mixing of dead space gas with alveolar gas. Phase III describes the so-called alveolar plateau representing CO₂-rich gas from the alveoli. In older infants and adults, phase III almost always has a slightly positive slope, indicating a rising PCO₂ due to the delayed emptying of alveoli with a low ventilation/perfusion ratio (high PCO₂). In ventilated newborns, this slope is rarely seen due to their typically fast exhalation times. An exaggerated positive slope is seen in patients with pulmonary inhomogeneity, high airway resistance, and/or mechanical obstruction of the airway as alveoli empty carbon dioxide at a variable rate in these conditions. This is discussed in more detail below. Phase IV is actually a component of phase I and describes the decrease of the exhaled CO₂ to zero at the beginning of inspiration.

12.2.2.2 $P_{et}CO_2$ Monitoring

Since capnography is noninvasive, its utilization to monitor gas exchange in ventilated infants, children, and adults is very attractive, and the most typical parameter monitored is end-tidal CO₂ ($P_{et}CO_2$). The various factors that increase or decrease $P_{et}CO_2$ are summarized in Table 12.6 (Shapiro and Kacmarek 1998).

Under ideal conditions, $P_{et}CO_2$ accurately represents alveolar PCO₂. However, this relationship is dependent on the delivery of carbon dioxide to the lung via the circulatory system (i.e., perfusion) and its removal from the lung (i.e., ventilation). Thus, the relationship between alveolar PCO₂ and $P_{et}CO_2$ is a reflection of the ventilation/perfusion ratio ($\dot{V} / \dot{Q}$) as assessed by the dead space to tidal volume ratio (V_D/V_T) (McSwain et al. 2010).

An important prerequisite for a $P_{et}CO_2$ measurement is the presence of a stable alveolar plateau at end expiration. Only if the capnogram shows such a plateau can we assume that the $P_{et}CO_2$ accurately reflects the alveolar PCO₂. However, in ventilated infants and some ventilated

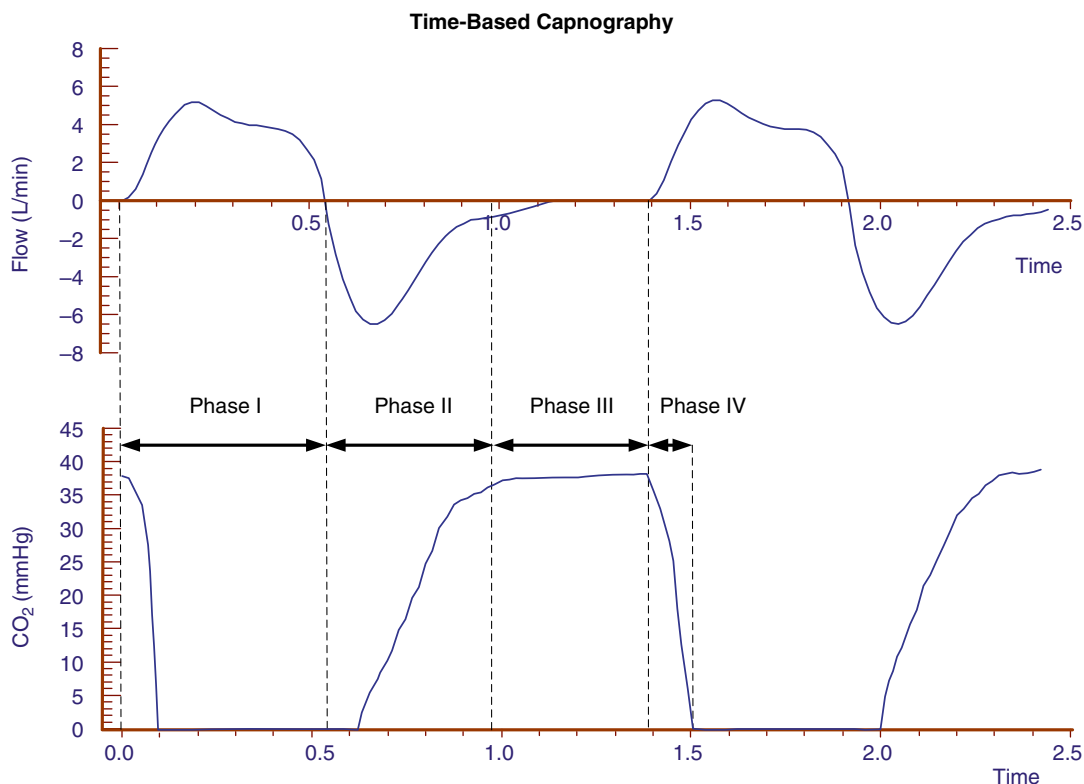


Fig. 12.8 A typical time-based capnogram of a ventilated neonate divided in 4 phases

Table 12.6 Clinical factors that affect $P_{\text{et}}\text{CO}_2$ (Shapiro and Kacmarek 1998)

	Increases $P_{\text{et}}\text{CO}_2$	Decreased $P_{\text{et}}\text{CO}_2$
CO ₂ -production and delivery to the lung	Increased by • fever • sepsis • bicarbonate administration • seizures	Decreased by • hypothermia • pulmonary hypoperfusion • cardiac arrest • pulmonary embolism • hemorrhage • hypotension
Alveolar ventilation	Decreased by • increased deadspace • hypoventilation • ventilatory inhomogeneity	Increased by • hyperventilation
Equipment malformations	• CO₂-rebreathing due to apparatus deadspace	• ventilator disconnection • esophageal intubation • complete airway/ endotracheal tube obstruction • poor gas sampling • too low response time • endotracheal tube leakage

children with increased airways resistance, this is not guaranteed as the adjusted expiratory time of the ventilator can be longer than the actual exhalation time of the patient (i.e., premature termination

of exhalation). In such a situation, there is no patient flow at end expiration (Fig. 12.9), and, thus, $P_{\text{et}}\text{CO}_2$ cannot be determined (Proquitte et al. 2004). Confounding variables do exist in the

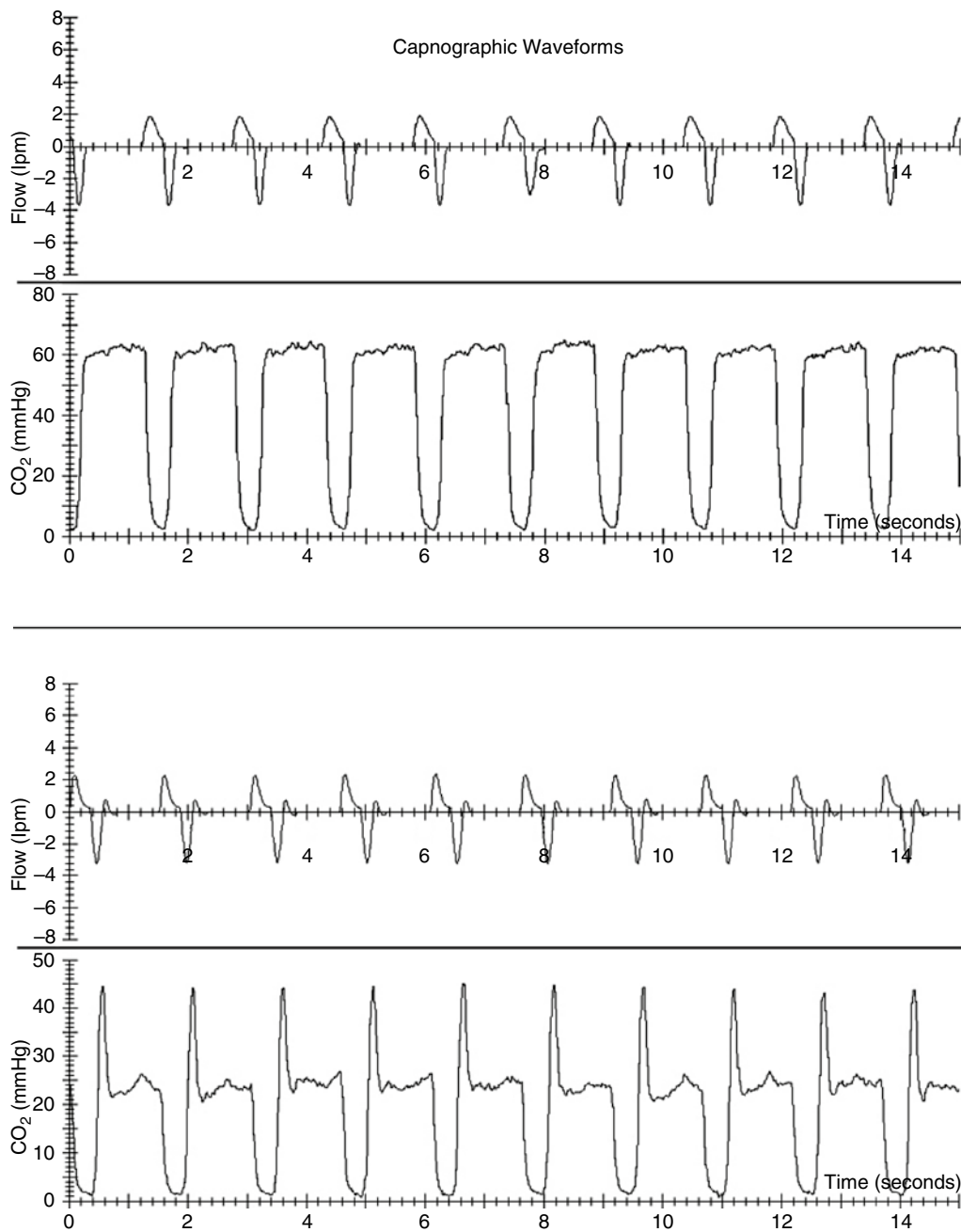


Fig. 12.9 Capnogram of a ventilated surfactant-depleted tracheotomized piglet with a stable alveolar plateau even during the expiratory pause (*top*) and a capnogram where

$P_{\text{et}}\text{CO}_2$ was falsified by CO₂ washout of the sample cell during the expiratory pause (*bottom*). Data from Proquitté et al. (2004)

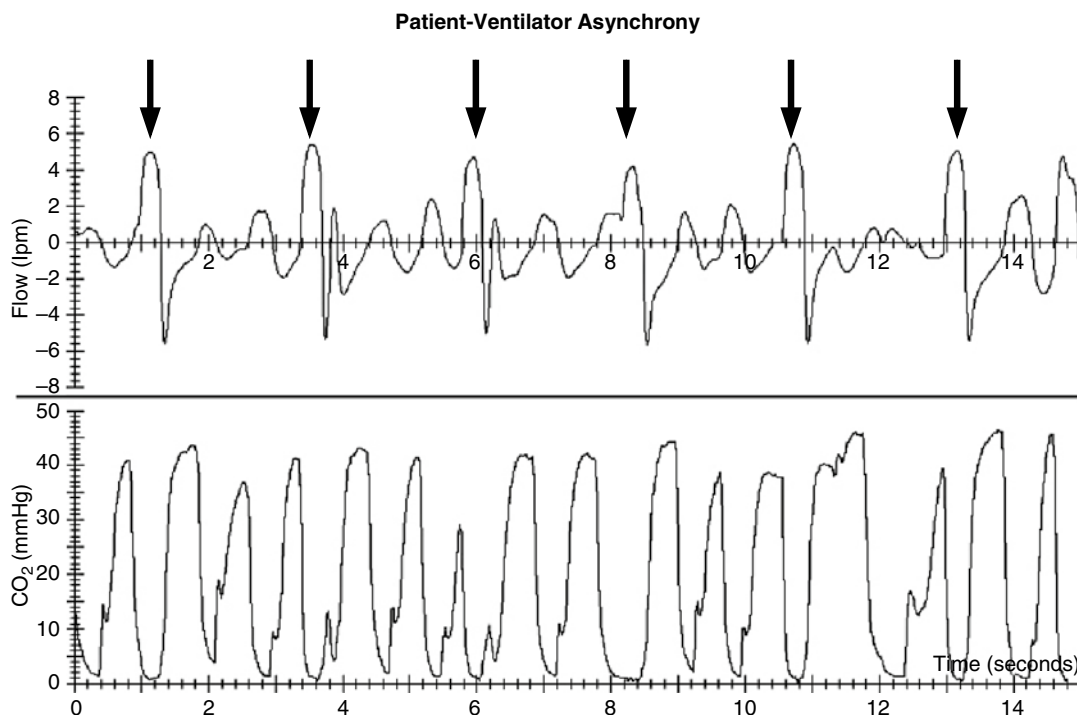


Fig. 12.10 Capnogram of a ventilated newborn with a mismatch of mechanical breath (*black arrows*) and spontaneous breathing

neonatal and pediatric populations. The presence of large endotracheal tube air leaks makes the measurement of “end-tidal” values less reliable (Schmalisch et al. 2012). Additionally, significant patient–ventilator dyssynchrony (Fig. 12.10) can make the accurate determination of $P_{\text{et}}\text{CO}_2$ difficult.

Therefore, $P_{\text{et}}\text{CO}_2$ measurements in ventilated patients are only useful if the shape of the capnogram is considered. Automated measurements of $P_{\text{et}}\text{CO}_2$ without monitoring the waveform should be used with caution as the resultant data can be misleading. Similarly, we should interpret $P_{\text{et}}\text{CO}_2$ values published in older literature with caution as the technical options for adequate monitoring of the capnogram were often very limited.

12.2.2.3 A Practical Approach to Interpreting Capnograms

What information can the capnogram offer the bedside clinician? At first, the presence of a physiologic meaningful $P_{\text{et}}\text{CO}_2$ should be assessed. If such a $P_{\text{et}}\text{CO}_2$ is not present, failure

to ventilate the patient’s lungs must be assumed. Table 12.7 summarizes typical causes of absent CO_2 elimination (Schmalisch 2004). Second, the shape of the capnogram must be compared with a typical pattern as shown in Fig. 12.8 by inspecting the inspiratory CO_2 baseline, steepness of phase II, alveolar plateau of phase III, and decline of the capnogram at the beginning of the next inspiration. Third, depending on the capnograph and the monitoring software utilized, the clinician should assess the characteristic parameters derived from the capnogram, for example, $P_{\text{et}}\text{CO}_2$, CO_2 elimination (VCO_2), $P_{\text{a-et}}\text{CO}_2$, and dead space (anatomic and alveolar).

12.2.2.3.1 The Inspiratory Baseline (Phase I)

Inspired gas should be void of carbon dioxide. Thus, the displayed CO_2 level should be zero; otherwise, there must be either rebreathing of CO_2 from the patient due to high apparatus dead space or the administration of exogenous carbon dioxide. Especially in very small infants, CO_2 rebreathing can occur if the tidal volume is

Table 12.7 Differential diagnostic causes of absent end-expiratory CO₂

	Patient	Capnograph
Immediately after intubation, CO ₂ absent or very minimal	• Inadvertent esophageal intubation	• Calibration error • Disconnection of the CO₂ analyzer or the sample tube
Exhaled CO ₂ present, then suddenly absent	• Accidental tracheal extubation • Disconnection of breathing circuit • Apneic spells • Cardiac arrest • Severe bronchospasm • Complete obstruction of ETT (e.g., mucous plugging or kinking)	• Disconnection of the CO₂ analyzer or the sample tube • Water condensation or secretions the CO₂ analyzer or in sampling tube • Failure of the capnograph

relatively low compared to the apparatus dead space. A leak around the endotracheal tube may reduce CO₂ rebreathing (Claure et al. 2003); however, it may dampen both tidal volume and $P_{a\text{CO}_2}$ measurements considerably (Schmalisch et al. 2012).

12.2.2.3.2 The Expiratory CO₂ Increase (Phase II)

During expiration, the first gas is eliminated from the CO₂-free anatomic dead space. Subsequently, in healthy lungs, the CO₂ curve rises with a steep upward slope. Phase II can be prolonged when the delivery of CO₂ from the lung is delayed, for example, due to pulmonary inhomogeneities, high resistances of the small airways, and mechanical obstructions, such as a blocked or kinked ETT. A prolonged phase II can also be caused by technical problems related to the capnograph. Technical limitations are most commonly seen in patients with stiff lungs and a low respiratory time constant when the response time of the capnograph is inadequate to follow the fast expiration.

12.2.2.3.3 The Alveolar Plateau (Phase III)

In adults and older infants, the shape of the alveolar plateau is one of the most interesting portions of the capnogram because the steepness of the slope is a function of morphometric structure and respiratory mechanics (Neufeld et al. 1992; Schwardt et al. 1991). Early phase III contains gas from the well-ventilated, low-resistance regions of the lung. Later in phase III, gas from poorly ventilated, high-resistance regions is exhaled which causes a slope of the alveolar plateau. Thus, the steepness of the alveolar plateau

is commonly used as an indicator for inhomogeneities in the alveolar time constants and $\dot{V}/\dot{Q}$ ratio (Ream et al. 1995). A flat phase III indicates relatively homogeneous exhalation from airways throughout the lung. It should be noted in very small infants that phase III should be interpreted with caution as the plateau (if it exists at all) is often small, and steepness is also a function of lung growth (Ream et al. 1995). Therefore, the diagnostic value of a phase III analysis in the small neonatal population may be limited. Nevertheless, the appearance of phase III in the capnogram indicates that alveolar gas has been sampled.

12.2.2.3.4 The Decrease of Exhaled CO₂ at the Beginning of Inspiration (Phase IV)

After expiration, the fresh gas from the breathing circuit rinses out the carbon dioxide from the previous exhalation. Thus, there should be a quick decrease of the end-expiratory CO₂ at the initiation of inspiration. Several techniques (e.g., tracheal gas insufflation) (Davies and Woodgate 2002; Miller et al. 2004) have been developed to reduce rebreathing and dead space ventilation such that the tidal volume is more efficiently used for gas exchange. However, for various reasons, these techniques have seen limited application in the neonatal and pediatric populations. A delayed decrease of the expired CO₂ may be caused by a respiratory circuit with low flow, such that CO₂ may accumulate in the inspiratory limb of the circuit. Furthermore, a prolonged phase IV can also be associated with technical failures of the capnograph (e.g., a slow response time of the CO₂ analyzer).

12.2.2.4 Relationship

Between $P_{\text{et}}\text{CO}_2$ and $P_{\text{a}}\text{CO}_2$

In infants with normal pulmonary function and well-matched $\dot{V}/\dot{Q}$, the $P_{\text{et}}\text{CO}_2$ can provide an accurate estimate of the PCO_2 in arterial blood ($P_{\text{a}}\text{CO}_2$) (Wu et al. 2003; McDonald et al. 2002; Bhat and Abhishek 2008), for all patient populations from the extremely low-birth-weight infant (Amuchou and Singhal 2006) through adults (McSwain et al. 2010; Wu et al. 2003; McDonald et al. 2002; Bhat and Abhishek 2008; Amuchou and Singhal 2006). Noninvasive measurement of $P_{\text{et}}\text{CO}_2$ clearly allows for an accurate estimation of $P_{\text{a}}\text{CO}_2$ in patients with minimal dead space ventilation without the inherent need for the time delay or the blood removal associated with performing an arterial blood gas analysis. The relationship between $P_{\text{et}}\text{CO}_2$ and $P_{\text{a}}\text{CO}_2$ in patients with elevated dead space is discussed in more detail below.

$P_{\text{et}}\text{CO}_2$ monitoring has several advantages for all patients requiring intensive care, from preterm newborns through elderly adults (McDonald et al. 2002; Rozycki et al. 1998), which include:

- Decreased blood loss by arterial sampling for blood gas analysis
- Lower risk of infection related to a decreased number of central venous line or arterial line entries
- Decreased costs
- Availability of continuous data

However, as shown in Table 12.6, several physiologic and technical factors as well as disease states can affect $P_{\text{et}}\text{CO}_2$ measurements and potentially make it less reliable as a surrogate for blood gas interpretation.

The lack of consistency in the agreement between $P_{\text{et}}\text{CO}_2$ and $P_{\text{a}}\text{CO}_2$ has led to significant controversy in the medical literature with regard to the usefulness of $P_{\text{et}}\text{CO}_2$ measurements in ventilated patients, especially in the neonatal population. McDonald et al. (2002) and Wu et al. (2003) have shown in large clinical studies in critically ill mechanically ventilated infants that $P_{\text{et}}\text{CO}_2$ correlates with $P_{\text{a}}\text{CO}_2$ and provides a clinically relevant, reliable estimation of ventilation for most infants. Similar results were found by Rozycki et al. (1998) investigating 45 newborn infants receiving mechanical ventilation. They suggest that

capnography in these patients may be useful for trending or screening patients for abnormal arterial CO_2 values. In contrast, Tobias et al. (Tobias and Meyer 1997a) found in intubated infants that $P_{\text{et}}\text{CO}_2$ does not accurately predict $P_{\text{a}}\text{CO}_2$ and that transcutaneous carbon dioxide ($P_{\text{tc}}\text{CO}_2$) measurements are more accurate. To the same result came Tingay et al. (2005) during neonatal transport as there was an unacceptable under-recording of the $P_{\text{a}}\text{CO}_2$ likely due to the technical limitations of the sidestream technology used.

A distinct improvement in the agreement between $P_{\text{et}}\text{CO}_2$ and $P_{\text{a}}\text{CO}_2$ was obtained by Kugelman et al. (2008) by using a double lumen endotracheal tube and a microstream sidestream capnograph. They demonstrated in 27 newborns (body weight 490–4,790 g) that distal end-tidal CO_2 measurements correlate significantly better with $P_{\text{a}}\text{CO}_2$ than when $P_{\text{et}}\text{CO}_2$ is measured with a mainstream capnograph. This improved agreement remained reliable in conditions of severe lung disease. However, such measurements can be difficult as the required cannula is small and may be occluded with secretions while continuously sampling. Unfortunately, the sampling equipment cannot be flushed with air to avoid damage to its filters.

Across a heterogeneous critically ill population of infants, children, and adolescents, McSwain et al. (2010) demonstrated a close correlation between $P_{\text{et}}\text{CO}_2$ and $P_{\text{a}}\text{CO}_2$. As a key component of their results, McSwain and colleagues noted that as dead space ($V_{\text{D}}/V_{\text{T}}$) increased, the mean gradient between $P_{\text{et}}\text{CO}_2$ and $P_{\text{a}}\text{CO}_2$ increased as physiology would dictate; however, the excellent correlation persisted. In contrast, a poor agreement between $P_{\text{et}}\text{CO}_2$ and $P_{\text{a}}\text{CO}_2$ in magnitude as well direction was observed in ventilated dogs undergoing thoracotomy (Wagner et al. 1998), during cardiac surgery (Russell et al. 1990), and neurosurgery (Grenier et al. 1999) and in mechanically ventilated adults with multisystem trauma (Russell and Graybeal 1994) due to highly variable $\dot{V}/\dot{Q}$ matching. A survey about misleading $P_{\text{et}}\text{CO}_2$ values during anesthesia and surgery has been provided by Wahba and Tessler (1996).

It appears that in neonatology (especially for the smaller preterm infants), $P_{\text{et}}\text{CO}_2$ measurements

may not be replacements for arterial or transcutaneous blood gases; however, in most of these patients, capnography can be helpful in monitoring the PCO_2 trend and assessing the integrity of the airway and ventilator circuit (e.g., monitoring for inadvertent extubation and circuit disconnections/blockages). Within the pediatric critical care environment, $P_{et}CO_2$ can be a suitable substitute for arterial blood gas analyses, if dead space ventilation and the expected gradient between $P_{et}CO_2$ and P_aCO_2 is considered (McSwain et al. 2010).

12.2.2.5 The $P_{a-et}CO_2$ Difference and Ventilation/Perfusion Abnormalities

$P_{et}CO_2$ is commonly lower than P_aCO_2 , and the difference ($P_{a-et}CO_2$) can be caused by $\dot{V}/\dot{Q}$ mismatching in the lungs (e.g., dead space ventilation) as a result of temporal, spatial, and alveolar mixing effects. The $P_{a-et}CO_2$ gradient is normally 4–6 mmHg, if ventilation and perfusion are reasonably matched. However, when the alveoli are not properly ventilated (i.e., shunt perfusion) or, much more significantly, when lung perfusion is decreased (globally or regionally) as compared to ventilation (i.e., dead space ventilation), the increased $\dot{V}/\dot{Q}$ mismatch will result in an increased $P_{a-et}CO_2$ difference. It should be noted that a variable air leak around the endotracheal tube or within the ventilator circuit (as discussed below), hypothermia, and other variables may result in a falsely decreased $P_{et}CO_2$ and, subsequently, an exaggerated $P_{a-et}CO_2$ gradient.

In several studies, the $P_{a-et}CO_2$ difference has been used to monitor $\dot{V}/\dot{Q}$ matching during mechanical ventilation. Wenzel et al. (1999a) found in ventilated rabbits a strong correlation between $P_{a-et}CO_2$ and alveolar dead space. Both increased significantly after surfactant depletion by bronchoalveolar lavage and decreased significantly after surfactant application with a return nearly to the baseline. Skimming et al. (2001) demonstrated in ventilated sheep that the vasodilator effects of nitric oxide (NO) inhalation improved the efficiency of CO_2 elimination in acutely injured lungs by a decrease in $P_{a-et}CO_2$, and these effects, including alveolar dead space, were relatively dose independent between 5 and

20 ppm. Due to the strong correlation between $P_{a-et}CO_2$ and alveolar dead space, these authors state that from a clinical perspective, measuring $P_{a-et}CO_2$ to monitor NO inhalation therapy is simpler than measuring alveolar dead space as an ordinary end-tidal CO_2 monitor can substitute for a sophisticated system of dead space measurements requiring simultaneous measurements of CO_2 elimination and tidal volume.

Hagerty et al. (2002) found a higher $P_{a-et}CO_2$ gradient when comparing newborns with pulmonary disease and those who received mechanical ventilation for non-pulmonary conditions. However, McDonald et al. (2002) showed in a large study in 129 ventilated infants using 2,184 arterial blood and gas samples that in most of the patients, $P_{a-et}CO_2$ is small enough such that $P_{et}CO_2$ monitoring enables the clinician to adequately monitor ventilation and gas exchange.

The $P_{a-et}CO_2$ difference can also be used as a minimally invasive monitor of pulmonary blood flow. A reduction in cardiac output causes a reduction in pulmonary blood flow, which produces a high $\dot{V}/\dot{Q}$ ratio and an increased alveolar dead space resulting in a lower $P_{et}CO_2$ and an increased $P_{a-et}CO_2$ difference. As pulmonary blood flow increases, thereby improving the $\dot{V}/\dot{Q}$ ratio, $P_{et}CO_2$ increases and $P_{a-et}CO_2$ decreases. Sanders et al. (1989) have shown that $P_{a-et}CO_2$ monitoring can be effectively utilized to predict successful resuscitation after cardiac arrest. During cardiac arrest, circulation and $P_{et}CO_2$ disappear. A subsequent increase in $P_{et}CO_2$ indicates effective cardiopulmonary resuscitation or return of spontaneous circulation. Berg and colleagues (1996) have confirmed these observations in an animal model.

In summary, an increase of the $P_{a-et}CO_2$ gradient is one of the most sensitive indicators of decreased pulmonary blood flow, which may be caused by acute pulmonary embolism (Napolitano 1999), air embolism, fat embolism, pulmonary hypertension, and/or, more commonly, a global decrease in cardiac output. Overall, poor cardiac output, decreased pulmonary blood flow for other reasons, and/or significant lung disease will result in high alveolar dead space, and, thus, $P_{a-et}CO_2$ will be increased. This is clinically seen as a poor correlation between $P_{et}CO_2$ and P_aCO_2 .

12.2.2.6 Alveolar Ventilation and Dead Space

Only one portion of the total delivered tidal volume from a ventilator participates in gas exchange with pulmonary capillary blood (i.e., alveolar ventilation). The difference between minute ventilation and alveolar ventilation is dead space ventilation—the portion of the delivered tidal volume of which gas exchange is negligible. Dead space consists of the conducting airways (anatomic dead space), the endotracheal tube and other adaptors (apparatus dead space), and the non-perfused or under-perfused alveoli (alveolar dead space). Anatomic and apparatus dead space may be combined into the term airway dead space. In ventilated neonates and young children, the dead space fraction (V_D/V_T) is higher than in adults which impairs both the alveolar ventilation and the homogeneity of the alveolar ventilation visibly by a higher lung clearance index (Schmalisch et al. 2006). Since areas of physiologic dead space (airway and alveolar) do not participate in gas exchange, expired CO_2 must derive from alveolar gas.

The first calculations of alveolar ventilation and airway dead space in neonates from the breathing gas were performed using the chemical CO_2 absorption method by Haldane and Scholander assuming that alveolar CO_2 can be approximated by the arterial CO_2 (Karlberg et al. 1954; Cook et al. 1957; Nelson et al. 1962). Chu et al. (1967) were the first to use a rapid capnograph to measure the $P_{\text{et}}\text{CO}_2$ in neonates and to calculate the anatomic and physiologic dead space using the Bohr equation:

$$V_{\text{Dana}} = V_T \frac{P_{\text{et}}\text{CO}_2 - P_{\text{mean}}\text{CO}_2}{P_{\text{et}}\text{CO}_2} \quad (12.3)$$

or the Bohr/Enghoff equation by substituting arterial CO_2 for $P_{\text{et}}\text{CO}_2$:

$$V_{\text{Dphys}} = V_T \frac{P_{\text{a}}\text{CO}_2 - P_{\text{mean}}\text{CO}_2}{P_{\text{a}}\text{CO}_2} \quad (12.4)$$

where mean $P_{\text{mean}}\text{CO}_2$ is the mean CO_2 tension of the mixed expired air. The difference of both dead space represents the alveolar dead space:

$$V_{\text{Dalv}} = V_{\text{Dphys}} - V_{\text{Dana}} \quad (12.5)$$

These calculations can be routinely used for all patient populations. It should be acknowledged that the calculation of the alveolar dead space requires simultaneous measurement of the arterial CO_2 tension ($P_{\text{a}}\text{CO}_2$), and the mixed expired carbon dioxide concentrations ($P_{\text{mean}}\text{CO}_2$) obviously limit the relative noninvasiveness of the technique as well as its ability to provide breath-to-breath information (Arnold 2001).

The Bohr and the Bohr/Enghoff equations use only three measured parameters to calculate dead space. Basing on earlier work by Aitken and Clark-Kennedy (1928), Fowler (1948) and Fletcher et al. (1981) were the first who considered the shape of the entire CO_2 curve during expiration for dead space calculations. They plotted exhaled CO_2 as a function of the exhaled volume and calculated different airway dead space from a single breath by the area under the curve as discussed in Sect. 12.2.3. This single-breath CO_2 (SBCO₂) technique is now commercially available and can be used for dead space measurements for all patient populations (McSwain et al. 2010; Ream et al. 1995; Riou et al. 2004).

Theoretically, Fletcher's method is optimal, provided that phases I–III are clearly defined. However, determination of dead space by the SBCO₂ method can be foiled if there is no alveolar plateau or if the transition from phase II to III cannot be clearly identified. This is predominantly a problem in very small lungs. Wenzel et al. (1999b) found in ventilated preterm infants that the SBCO₂ technique failed in 67 % of the infants studied. In contrast, the dead space calculations by the Bohr or the Bohr–Enghoff equations are independent of the shape of the volumetric capnogram and are preferentially used by several authors for dead space calculation (Ream et al. 1995; Rozycki et al. 1998; Arnold et al. 1993, 1995; Lum et al. 1998). However, this advantage may be deceptive because until recently it has not been known to what extent the missing alveolar plateau leads to dead space errors. As such, the failure rate of capnography to determine dead space as well as

the calculated dead space itself may depend on the method used (Wenzel et al. 1999b).

12.2.2.7 Specific Considerations During Noninvasive Ventilation

Noninvasive ventilatory support (i.e., ventilation without intubation), including noninvasive ventilatory pressure ventilation (NPPV) and continuous positive airway pressure (CPAP), has been successfully applied to patients with acute or acute-on-chronic respiratory failure of various etiologies. During recent several years, there is a clear shift to noninvasive respiratory support in all patient populations as it has become widely accepted as an effective means to improve pulmonary and non-pulmonary outcomes, including a reduction in the risk of ventilator-induced lung injury (VILI) (Davis et al. 2009; Mahmoud et al. 2011). In preterm infants, the use of noninvasive CPAP for respiratory support has provided an improvement in survival rates and morbidity, compared to endotracheal intubation (Gittermann et al. 1997; Dani et al. 2004; Geary et al. 2008; Morley et al. 2008). Unfortunately, definitive data are lacking in the pediatric population. In the adult population, noninvasive ventilation has been demonstrated to reduce mortality, ventilator-associated pneumonia (VAP), and intubation rates (Keenan et al. 2004; Hess 2005).

In addition to improvements in lung mechanics and gas exchange, noninvasive ventilation aims to reduce CO₂ rebreathing by the flushing of airway dead space and to improve alveolar gas exchange by a reduction of alveolar dead space. Theoretically, capnography should be a suitable method to monitor the effectiveness of this therapy. However, capnography is only rarely used during noninvasive-ventilator support due to the very difficult measuring conditions. The patient interface (e.g., binasal prongs, nasopharyngeal tubes, or masks) limits the usefulness of the capnographic measurements as exhaled CO₂ is diluted by the driving inspiratory flows of the system and accurate measurements are limited by the leakage of expired gas around the monitoring device (as described in more detail below). Both

of these limitations of noninvasive ventilation hamper precise measurements.

Due to these technical difficulties, there are only a few reports of the use of capnography during noninvasive ventilation in the medical literature, mainly in adults. Schettino et al. (2003) used mainstream capnography in an in vitro model to optimize face masks for adults with regard to CO₂ rebreathing. Henke et al. (1991) investigated the effect of CPAP in sleeping adults with obstructive airways by $P_{et}CO_2$ sidestream measurements, and Bratzke et al. (1998) compared controlled mechanical ventilation (CMV) with CPAP during anesthesia using $P_{et}CO_2$ and dead space measurements.

Capnographic measurements in neonatal/pediatric animal models have been performed using the combination of intubation with noninvasive devices to facilitate CO₂ measurements. Miller et al. (2004) investigated the effect of tracheal gas insufflation-augmented CPAP on CO₂ elimination in intubated piglets, and Pillow et al. (2007) compared bubble CPAP with constant pressure CPAP using mainstream capnography in intubated preterm lambs. Thus, the efficiency of ventilatory support in most studies of non-intubated patients is assessed by conventionally measured arterial blood gas analyses, transcutaneous monitoring, and/or pulse oximetry (Gozal 1997; Criner et al. 1999; Regnis et al. 1994).

As previously noted, a principal difficulty of capnography with noninvasive ventilatory support is that the site of CO₂ and air flow measurements depends on the patient interface used (e.g., facial mask, head box, mono- or binasal prongs, or pharyngeal tubes). With all of these patient interfaces, large air leaks can occur. When using nasal prongs, oral air leaks can lead to highly variable leak flows which prevent reliable CO₂ and air flow measurements. Hückstädt et al. (2003) performed air flow measurements in 69 neonates during nasal CPAP using differential pneumotachography, and in 49 (71 %) infants, measurements were not possible due to uncorrectable air leaks. In contrast to measurements of ventilation during noninvasive ventilatory support (Fischer et al. 2008, 2009;

Schmalisch et al. 2009), nothing is known about the effect of air leaks on the measured $P_{\text{et}}\text{CO}_2$ or dead space. Overall, capnography during noninvasive ventilation support seems to be highly doubtful, and, therefore, it cannot be recommended for clinical use at this time.

12.2.2.8 Specific Considerations in the Neonatal Patient

The developing neonatal lung differs in many respects from older children and adults, and this may influence CO_2 measurements significantly. It is essential to understand these age-related deviations to minimize misleading interpretations of a capnogram.

12.2.2.8.1 Small Airways

In healthy adult lungs, there is a rapid rise in CO_2 concentration during phase II of the capnogram with only a negligible contribution of the upper airways to gas exchange. In neonates, the diameter of the airways is inherently much smaller. The smaller the airway diameter, the higher is the impact on the exhaled CO_2 . With a larger airway diameter, the ratio between inner surface and volume suffices to prevent a fast CO_2 exchange between gas and tissue. However, in much smaller airways, there is already an inner-bronchial PCO_2 exchange. This may explain why neonates have an exaggerated phase II and a reduced, or even missing, phase III (Tirosh et al. 2001).

12.2.2.8.2 Lung Growth

Lung growth during infancy also affects phase III (if even present) of the capnogram. Ream et al. (1995) found a steeper slope of phase III in small infants as compared to adults. This result is supported by the modeling studies of Schwardt et al. (1991) and Neufeld et al. (1992) which demonstrated that a morphometric decrease of the airway cross-section is associated with an increase in the diffusional resistance within the airways resulting in an increase in the phase III slope. However, the steeper phase III, the more difficult it is to distinguish between phase II and III, and the more difficult becomes the calculation of the dead space from the volumetric capnogram by Fletcher's method.

12.2.2.8.3 Respiratory Time Constant

The main problem of capnography in ventilated neonates is the fast exhalation time such that the response time of the capnograph may not be sufficient to reach an alveolar plateau in the capnogram. This is especially true in preterm newborns with stiff lungs where the respiratory time constant can be shorter than 50 ms and exhalation completed within 200 ms. The influence of the stiffness of the lungs on the incidence of capnograms without alveolar plateau was investigated by Proquitté et al. (2004) in 21 ventilated surfactant-depleted piglets (body weight 560–1,435 g). This study noted that the incidence of capnograms without alveolar plateau increased considerably with decreasing exhalation time. If the exhalation time was shorter than 200 ms, an alveolar plateau was not seen in more than 75 % of all recorded files. This agrees well with a study by Tirosh et al. (2001) which demonstrated that with decreasing gestational age, the number of capnograms without alveolar plateau increased significantly.

12.2.2.8.4 Breathing Pattern

Relatively higher respiratory rates and smaller tidal volumes encountered in neonates, as compared to older infants and adults, make capnography much more difficult. Technical requirements of the capnograph for use in neonates and small children are higher and include:

- Minimal dead space of mainstream sensors because of the lower delivered tidal volumes
- Low suction flow of sidestream monitors because of the low expiratory flow rates
- Fast response time of the CO_2 analyzer because of the short exhalation times, especially in preterm neonates with stiff lungs
- High sample rate of the signals to obtain sufficient graphic resolution of the capnogram, especially in infants and young children with elevated respiratory rates

The concept of capnography was initially developed for adults with a well-defined capnogram. Ventilation and gas exchange in smaller lungs may differ from adult lungs in many respects. Particularly in premature neonates, in which the phase II is widened and phase III reduced or

absent, we will need imaginative physiologic concepts to interpret such capnograms.

12.2.2.9 Current Technical Limitations of Capnography in the Neonatal Patient

An important difference of capnography in ventilated newborns compared to older infants, children, or adults is the use of uncuffed endotracheal tubes (ETT). This practice leads to air leakages around the ETT which are observed in about 70 % of all ventilated neonatal infants (Bernstein et al. 1995). In the past, several studies were performed to investigate the effect of ETT leakages on the measurement of ventilation and lung mechanics and to develop suitable correction algorithms (Schmalisch et al. 2009; Kondo et al. 1997; Herber-Jonat et al. 2008); however, little is known about the effects of ETT leaks on capnographic measurements. Depending on the used ventilator, tidal volume measurements are reliable up to 5–20 % endotracheal tube air leaks (Mahmoud et al. 2009). In contrast to volume measurements, it is not possible to give an upper limit of ETT leaks which may be tolerated for capnographic measurements with clinically applicable results. The leak-dependent CO₂-measuring error depends on the shape of CO₂ plateau in the exhaled air. If there is a wide alveolar plateau, capnographic measurements may be reliable for ETT leaks up to 20 % (Schmalisch et al. 2012). However, in mechanically ventilated newborns with low compliant, stiff lungs, there is only a small (if any) CO₂ plateau at the end of expiration. Therefore, the presence of ETT leak in these infants' capnographic measurements should be interpreted with caution, and the $P_{a\text{CO}_2}$ is the most falsified capnographic parameter by the ETT leak.

One of the most important obstacles in the use of mainstream capnography in ventilated newborns is the additional dead space of the CO₂ analyzer chamber. For most neonates, current technology allows for the use of capnography. However, in preterm infants with low tidal volumes, rebreathing of exhaled CO₂ with the potential of generating false inspiratory and expiratory CO₂ measurements may occur. This was a significant problem in the past using volumetric cap-

nography by serial connection of a CO₂ analyzer and a flow sensor where the resulting dead space could exceed 30 % of the tidal volume (Wenzel et al. 1999b). Combined sensors for volumetric capnography are now available (e.g., neonatal sensor of the NM3, NICO, and CO₂SMO+ respiratory monitors, Philips Respironics, Murrysville, PA, USA) with dead space of about 1 mL. Except for premature neonates, these new flow sensors have essentially eliminated the dead space concern of the capnostats. If the tidal volume is less than 5 mL (e.g., ventilated preterm newborn <1,000 g), a dead space of 1 mL is an undesirable load (Nassabeh-Montazami et al. 2009).

Sidestream measurements are dead space-free, and special microstream devices (e.g., NBP-75, Nellcor Puritan Bennett, Pleasanton, CA, USA) have been developed for use in neonates with low sampling flows and rapid response times (Hagerty et al. 2002; Kugelman et al. 2008). When a sidestream capnograph is used, the sampling tube needs special care to prevent measuring errors. During mechanical ventilation, water droplets and secretions can be aspirated, significantly affecting accuracy of the carbon dioxide measurements. In the extreme situation, the sample port or the sampling tube can become completely occluded.

Some capnographs either increase the sampling flow or, to clear contaminants from the tube, reverse the flow (purge) when they sense a drop in pressure from a flow restriction. If this fails, the sampling port and/or the tubing requires replacement. Occasionally, liquids enter the CO₂ analyzer chamber despite the presence of a water trap. This can affect the performance of the CO₂ monitor and produce abnormal capnograms. It should be noted that cleaning the CO₂ analyzer chamber can be difficult. Positioning of the sampling tubing upwards (i.e., away from the patient and against gravity) decreases the risk of liquids entering in the tubes and the analyzer chamber. When abnormal capnograms are noted, clinicians should ensure that there is no system fault. In clinical practice, a common, but less accurate, bedside method to check the capnograph is to record a normal CO₂ tracing (e.g., one's own) to confirm the proper functioning of the capnometer (Bhavani-Shankar et al. 1992).

Independent of which measuring principle is used, the response time of the capnograph must be sufficiently high so that the magnitude and shape of the signal are not falsified. Due to the short respiratory time constants in neonates and young infants, a capnograph should have an adequate response time, which has two components—transit time and rise time (Tang et al. 2005).

In sidestream measurements, the transit time is the time taken by the gas sample to travel from the sample port to the CO₂ analyzer and depends on ventilator pressures, suction flow, and length and diameter of the tube. The transit time can be numerically corrected provided that it is nearly constant. Nevertheless, a volumetric capnograph is hardly possible due to remaining errors in the synchronization of the volume and CO₂ signals.

The rise time is the time of the CO₂ analyzer taken from 10 to 90 % of the final value. Unfortunately, the possibilities of improving the rise time by signal filtering are marginal and are limited by the rapid increase of the noise in the signal (Wong et al. 1998). Capnographs used in neonates currently have rise times ($T_{10-90\%}$) of 50–80 ms depending on the airflow used for testing. This can be too long for preterm neonates with low expiratory flow and respiratory rates of 60/min and higher (i.e., expiratory time, t_E , <500 ms). If the rise time of the capnograph is too high as compared to the exhalation time, the alveolar plateau is not reached and $P_a\text{CO}_2$ is underestimated. Therefore, older results using capnographs with much higher rise times should be viewed with reservation.

As many capnographs are developed for children and adults with a relatively low sampling rate of the signals, the specifics of the technology used must be assessed before employing such devices in the neonatal and infant populations. A sampling rate of 50/s for CO₂ and gas flow may be sufficient in adults with an expiratory time of several seconds; however, such a sampling rate would provide only 25 sample values in a preterm newborn with an expiratory time of 500 ms. Such a situation would put into doubt the ability to cleanly distinguish phase I, II, and III of the capnograms. To accurately record breathing signals of premature infants, a

sampling rate of at least 200 Hz is required. For full-term neonates and infants, a sampling rate of 100 Hz is generally adequate. These limits are necessary for a precise evaluation and an accurate graphic presentation of the signals (Bates et al. 2000). As already shown, the graphic assessment of a capnogram is an essential prerequisite for a valid interpretation of capnogram-derived parameters.

12.2.2.10 Time-Based Capnography and Endotracheal Tube Placement

Although practical applications of end-tidal CO₂ monitoring in the ICU setting include adequacy of alveolar ventilation during mechanical ventilation and respiratory monitoring of spontaneously breathing patients, one could argue that the most important use for this monitoring technology in the ICU setting is to assess proper endotracheal tube (ETT) positioning and patency. The use of capnography at intubation for a rapid assessment of appropriate ETT placement by confirming the presence of exhaled carbon dioxide is standard of care. Knapp et al. (1999) demonstrated capnography as the most rapid and reliable method for evaluation of appropriate ETT placement (Clark et al. 1992). One could argue that capnography should be used through the duration of mechanical ventilation to ensure the continued integrity of the ventilatory system (Cheifetz and Myers 2007). However, only a small subset of centers use capnography throughout the duration of mechanical ventilation to monitor for inadvertent ETT dislodgement or discontinuity of the ventilator circuit. It should be noted that volumetric capnography, as described below, is a more sensitive indicator of appropriate ETT placement than time-based (i.e., end-tidal CO₂) monitoring.

12.2.3 Volume-Based (Volumetric) Capnography

With volume-based or volumetric capnography, a Capnostat (i.e., carbon dioxide sensor) and a pneumotachometer (i.e., gas flow sensor) in combination measure the quantity of CO₂ exhaled as

a function of the total expired volume of gas. The net quantity of CO_2 expired (VCO_2) is calculated and expressed as a volume of gas, generally in units of mL/min, rather than as a gas fraction or partial pressure (as occurs with time-based capnography). In the unusual circumstance in which carbon dioxide is present in the inspired gas, the difference between inspired and expired carbon dioxide is used to calculate VCO_2 . Volumetric capnography would be expected to be an improved indicator of dynamic changes in gas exchange as compared to time-based capnography (Proquitt et al. 2004; Schmalisch 2004).

Volumetric capnography is often referred to as single-breath carbon dioxide (SBCO_2) elimination because the quantity of carbon dioxide eliminated per breath is used for most of the calculations. The SBCO_2 waveform includes three distinct phases enabling clinicians to assess clinical issues of cardiorespiratory concern (see Fig. 12.11). Phase I depicts gas exhaled from the upper airways (i.e., gas exhaled from the combined anatomic and apparatus dead space), which is generally void of carbon dioxide. An increase in the duration of phase I is consistent with an increase in anatomic/apparatus (i.e., airway dead space) dead space. As an example, a prolongation of phase I can be seen with excessive PEEP leading to distension of the upper airways. Phase 2 depicts a transitional phase of ventilation from the upper to the lower airways

and tends to depict alterations in perfusion. A slower rise of phase 2 tends to correlate with decreased pulmonary capillary blood flow. Phase 3 represents alveolar gas exchange and may indicate abnormalities in gas distribution due to heterogeneous lower airway and/or alveolar disease. An upsloping of phase 3 generally indicates maldistribution of gas delivery throughout the lung regions. Such an upsloping can be seen with significant lower airways disease (i.e., bronchospasm).

12.2.3.1 Technique

Volumetric capnography is the continuous monitoring of carbon dioxide elimination per unit time. CO_2 elimination (VCO_2) is affected by ventilation, circulation/pulmonary perfusion, and, to a much lower degree, diffusion as carbon dioxide diffuses so rapidly across the epithelial–endothelial junction. Carbon dioxide elimination can be a valuable clinical marker for acute changes in the cardiorespiratory status of an invasively ventilated patient. Basic physiology states that VCO_2 indicates pending alterations in $P_a\text{CO}_2$.

Devices that monitor VCO_2 and display volumetric capnograms provide bedside clinicians with a breath-by-breath indicator of gas exchange in response to changes in a patient's cardiorespiratory status in relation to variations in the trajectory of clinical illness and/or in response to alterations in the medical management of a patient (Taskar et al. 1995). Overall, volumetric capnography provides a global picture of the physiologic effects of cardiorespiratory interactions for the mechanically ventilated patient.

12.2.3.2 Carbon Dioxide Production/ Metabolism

An underlying principle of capnography (time-based and volume-based) is that carbon dioxide elimination and carbon dioxide production must always equilibrate, with carbon dioxide production being primarily determined by cellular metabolism. Normally, carbon dioxide production is dependent on a person's activity level and weight. For a resting, healthy, normal person with a respiratory quotient of 0.8, carbon dioxide production minute is estimated by Brody's formula, $8 \times \text{patient weight}^{0.75}$, where CO_2 production is

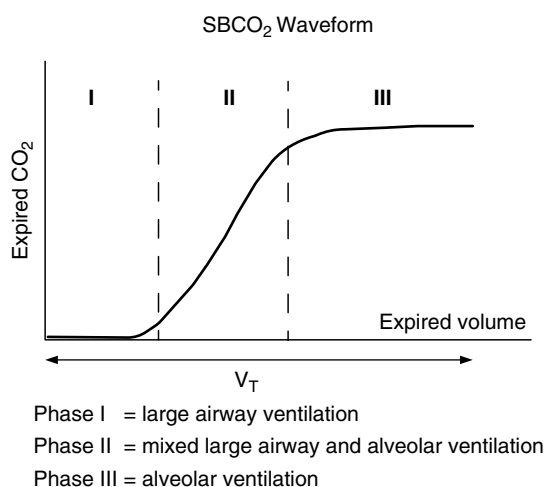


Fig. 12.11 Single breath carbon dioxide (SBCO_2) waveform

calculated in mL/min and patient weight is measured in kilograms. Thus, an average size, resting adult produces carbon dioxide at approximately 200–250 mL/min (Arnold et al. 1993). However, there are no equations to predict carbon dioxide production for an invasively ventilated patient, who may have injured lungs and be pharmacologically sedated as Brody's formula simply does not apply. Thus, it is important to stress that much of the interpretation of volumetric capnography is based on trends over time and patterns of change rather than absolute numbers.

Clinical conditions which directly affect metabolism would be expected to predictably decrease or increase CO_2 production accordingly. Thus, CO_2 production decreases with pharmacologic sedation, natural or pharmacologic sleep, and hypothermia (except if shivering occurs) and increases with agitation, fever, shivering, and excessive caloric intake.

Carbon dioxide balance in the body (i.e., production versus elimination) at any point in time is dependent on the intricate balance between CO_2 production, transport (cells to blood, then to lungs), storage (skeletal muscle, fat, and bone), and exhalation. In a normal, healthy individual, CO_2 produced from metabolism rapidly equilibrates with CO_2 elimination via the lungs. However, the time to re-equilibration can vary greatly with the degree of alterations in pulmonary capillary blood flow and/or lung volume. Thus, acute changes in VCO_2 and the return to an equilibration with carbon dioxide production will vary in relation to both the timeframe and magnitude of the cardiorespiratory change(s). This time variability can be a hurdle in the interpretation of volumetric capnography.

12.2.3.3 Clinical Applications

The volumetric capnogram (i.e., single-breath carbon dioxide waveform) has been successfully used in the measurement of anatomical dead space, pulmonary capillary perfusion, global cardiac output, and effective ventilation (Arnold et al. 1993; Blanch et al. 2006). By analyzing

volumetric capnograms, clinicians can easily and quickly assess cardiorespiratory issues of concern. In Fig. 12.11, phase 1 represents gas exhaled from the upper airways (i.e., gas exhaled from anatomic dead space), which is generally void of carbon dioxide (Proquitte et al. 2004). Therefore, an increase in phase 1 indicates an increase in anatomic dead space ventilation (V_{Dana}). Such a situation can occur with excessive PEEP, which may overdilate the upper airways (as well as the alveoli). Phase 2 is the transitional phase from upper to lower airway ventilation and tends to depict changes in perfusion. For example, a decrease in phase 2 slope would be indicative of reduced perfusion. Phase 3 is the area of alveolar gas exchange and represents changes in gas distribution. For example, an increase in the slope of phase 3 is indicative of increased maldistribution of gas delivery.

As with oxygen consumption, CO_2 production and elimination (VCO_2) is a continuous process. VCO_2 rapidly reflects changes in both ventilation and perfusion regardless of clinical etiology. As such, VCO_2 reflects the body's physiologic response to changes in a patient's cardiorespiratory status and can be a useful monitor to assess response to changes in mechanical ventilator settings as well as therapies that affect pulmonary perfusion (including global cardiac output). Thus, volumetric capnography is a sensitive clinical tool useful for reflecting acute changes in the cardiorespiratory status and metabolic state of a mechanically ventilated patient (Breen et al. 1996a, b), as discussed in more detail below.

12.2.3.3.1 Endotracheal Intubation

Although time-based capnography has become the standard of care for determining endotracheal intubation (Holland et al. 1993; Birmingham et al. 1986; Knapp et al. 1999; Anonymous 2006), one could speculate that volumetric capnography would be superior as it provides data on both carbon dioxide elimination and the movement of gas flow in and out of the airways (Sum-Ping et al. 1989; Grmec 2002). It should be noted that

time-based capnography can provide false-positive results for the determination of endotracheal intubation when carbon dioxide is present in the stomach. Although somewhat rare, this typically occurs after ingestion of a carbonated beverage or prolonged bag-mask ventilation. Volumetric capnography would be much less likely to provide a false-positive result as expiratory gas flow would be unlikely to be detected with a misplaced endotracheal tube.

12.2.3.3.2 Mechanical Ventilation

Volumetric capnography may assist the clinician in managing the mechanical ventilator as changes in $\dot{V}CO_2$ predict changes in P_aCO_2 . As the patient's exhalation of carbon dioxide increases (i.e., increased $\dot{V}CO_2$), the level of carbon dioxide in the blood must decrease (i.e., decreased P_aCO_2). Likewise, any decrease in $\dot{V}CO_2$ would predict an increase in P_aCO_2 . As P_aCO_2 obviously cannot decrease to zero or increase to infinity, the changes seen in $\dot{V}CO_2$ and P_aCO_2 must be transient until carbon dioxide elimination re-equilibrates with carbon dioxide production. One of the more difficult aspects of utilizing volumetric capnography in the clinical setting is evaluating the variable of time. The time for re-equilibration of CO_2 production and elimination varies with the patient's clinical status as well as the degree and timing of ventilator changes. Baseline lung volume and changes in lung volume are an inherent component of the required equilibration time.

Although data are limited, it would be anticipated that volumetric capnography could assist with PEEP management as lung volume is a key component of carbon dioxide elimination. As the lung collapses or overdistends, carbon dioxide elimination would be anticipated to decrease. In contrast, carbon dioxide elimination would be expected to increase as the lung approaches a more optimal lung volume. Although this concept is based on physiology, clinical application becomes difficult as the time to CO_2 re-equilibration is considered. A more detailed dis-

cussion of PEEP titration by the use of volumetric capnography is beyond the scope of this chapter.

From a weaning perspective, volumetric capnography may provide objective data to assist clinicians. Successful weaning using volumetric capnography is demonstrated by an increase in spontaneous alveolar minute ventilation in association with a stable (or slightly increased) elimination of carbon dioxide. If seen, an increase in $\dot{V}CO_2$ with weaning often correlates with an increase in CO_2 production (i.e., increased respiratory muscle activity) with the patient being able to exhale the additional carbon dioxide produced. In such situations, an arterial blood gas would demonstrate a stable P_aCO_2 . A significant increase in $\dot{V}CO_2$ with weaning from mechanical ventilation would suggest excessive work of breathing and the potential for impending respiratory decompensation. This scenario would be consistent with a visual assessment of increasing respiratory distress (e.g., retractions, tachypnea, and potentially agitation).

With the failure of weaning from mechanical ventilation as the ventilator settings are decreased, the patient is no longer able to maintain an adequate degree of spontaneous ventilation, and, hence, total minute ventilation falls. This decrease in minute ventilation is associated with a decrease in carbon dioxide elimination, and an arterial blood gas would, thus, reveal an elevated P_aCO_2 . Volumetric capnography enables the bedside clinician to more easily and quickly identify weaning failure and, in response, increase mechanical ventilator support promptly and often without the requirement for an arterial blood gas determination.

12.2.3.3.3 Pulmonary Blood Flow

Physiology dictates that any clinical condition which alters pulmonary blood flow will alter CO_2 elimination. A decrease in pulmonary capillary blood flow (regardless of etiology) results in a decrease in $\dot{V}CO_2$. Such conditions include a decrease in RV output (which would include a

decrease in global cardiac output), pulmonary hypertension, and/or pulmonary (including thrombus, fat, and air) embolus. VCO_2 can be used as an effective monitor for pulmonary blood flow as long as minute ventilation is stable.

One of the key difficulties of volumetric capnography occurs when there are competing cardiorespiratory variables. For example, if pulmonary capillary blood flow increases (which should increase VCO_2) and minute ventilation decreases (which should decrease VCO_2 as described above), then VCO_2 will move in the direction of the primary pathophysiology, which the clinician must then determine. The same would be true for a decrease in pulmonary blood flow and an increase in minute ventilation or other competing physiologic changes.

12.2.3.3.4 Assessment of Dead Space Ventilation

One of the most important applications of volumetric capnography is the calculation of physiologic dead space and the total dead space to tidal volume ratio (V_D/V_T) (see Eqs. 12.3. and 12.4). Total physiologic dead space equals airway (anatomic and apparatus) dead space plus alveolar dead space. Thus, alveolar dead space can be calculated once one knows the V_D/V_T ratio, delivered tidal volume, and airway dead space. It should be noted that although volumetric capnography is generally a noninvasive monitoring technique, the calculations of physiology dead space and the V_D/V_T ratio do require an arterial blood gas.

The V_D/V_T ratio has been successfully used to predict extubation readiness in a heterogeneous population of infants and children as reported by Hubble et al. (2000). A V_D/V_T ratio of less than 0.50 correlated with a 96 % chance for successful extubation, while V_D/V_T ratios of 0.51–0.65 and greater than 0.65 correlated with successful extubation rates of 60 and 20 %, respectively. The V_D/V_T ratio has also been used to assess the survival likelihood of adult patients with acute respiratory distress syndrome with a $V_D/V_T \leq 0.55$ representing increased survival (Kallet et al. 2004; Nuckton et al. 2002).

Essentials to Remember

- Capnography is an essential monitoring system for critically ill patients and is increasingly being described as the fifth vital sign.
- Time-based capnography represents carbon dioxide elimination as expressed as CO_2 partial pressure or CO_2 fraction over time. Volume-based (volumetric) capnography represents carbon dioxide elimination over exhaled volume.
- Recent technologic advances have allowed for noninvasive carbon dioxide monitoring for all patient populations, although limitations do exist for the small premature infant.
- The clinical use of carbon dioxide monitoring should allow for decreased blood loss related to a lower need for arterial sampling for blood gas analysis, lower risk of infection related to a decreased number of central venous line or arterial line entries, decreased costs, and availability of continuous data.
- Both time-based and volume-based capnography provides clinical information concerning both ventilation and perfusion. Overall, volumetric capnography provides a global picture of the physiologic effects of cardiorespiratory interactions.
- Basic physiology states that carbon dioxide elimination (VCO_2) indicates pending alterations in the arterial carbon dioxide concentration ($P_a\text{CO}_2$).
- Much of the interpretation of volumetric capnography is based on trends over time and patterns of change rather than absolute numbers.
- Elevated dead space to tidal volume ratio (V_D/V_T) has been correlated with extubation failure in the pediatric population and increased mortality in the adult ARDS population.

12.3 Transcutaneous Carbon Dioxide Monitoring in Infants and Children

Joseph D. Tobias

Educational Aims

- The reader will be familiar with the various techniques available for the continuous, noninvasive monitoring of PCO_2 .
- The reader will understand the advantages and disadvantages of the different techniques for continuous monitoring of PCO_2 .

12.3.1 Introduction

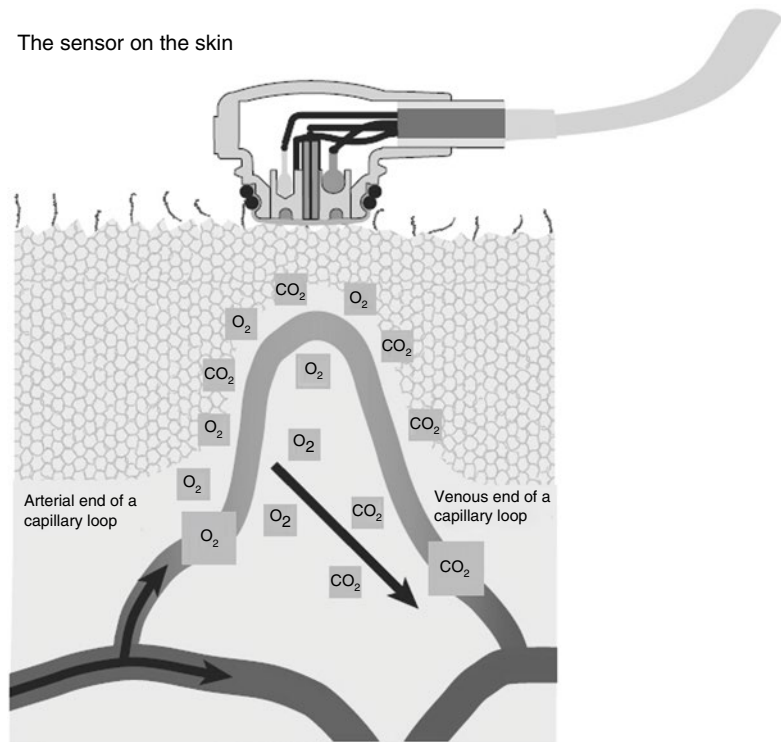
The equipment and techniques to accurately measure transcutaneous PCO_2 (TC- CO_2) were first developed and described in 1960 by Dr. Severinghaus (Severinghaus 1960). This pioneering work was later applied to clinical trials which demonstrated a linear correlation between skin surface PCO_2 and arterial CO_2 ($P_a\text{CO}_2$) in the range of 20–74 mmHg (Johns et al. 1969). The initial investigations involving TC- CO_2 monitoring were performed using a specially designed temperature-stabilized tissue PCO_2 electrode. However, it was later determined that it was feasible to noninvasively and continuously measure transcutaneous oxygen (TC- O_2) and later TC- CO_2 by using an electrode that provided local heating of the skin. The initial applications of these devices were in the neonatal population in whom the continuous monitoring of PO_2 was necessary to limit the deleterious effects of excessive tissue oxygen concentrations on the eye (Eberhard et al. 1976). Similar technology was subsequently applied to the continuous measurement of TC- CO_2 thereby resulting in the commercially available monitors which combined the ability to provide the continuous measurement of TC- O_2 and CO_2 being introduced into clinical practice in the 1980s (Eberhard and Schafer 1980). Although

the largest application of TC- CO_2 monitoring remains in the neonatal population (Cassady 1983), a greater appreciation of the potential utility of this technology has resulted in several potential applications outside of the newborn population. Suggested applications outside of the neonatal population have included continuous CO_2 monitoring during mechanical ventilation including high-frequency oscillatory ventilation, in spontaneously breathing patients with respiratory insufficiency related to various pathologic processes, during noninvasive ventilatory support, with apnea testing during brain death examination, and in the assessment of patients with diabetic ketoacidosis (DKA) (Tobias 2009).

12.3.2 Technical Aspects of Transcutaneous Carbon Dioxide Monitoring

TC- CO_2 monitors apply heat (42–43 °C) to the skin to induce vasodilatation of the capillary bed which results in the equilibration of capillary and arterial PCO_2 levels (Fig. 12.12). Capillary vasodilatation also facilitates the diffusion of CO_2 from the capillary lumen to the membrane of the TC- CO_2 monitor. This externally applied heat alters the true value of the capillary/arterial PCO_2 by changing the solubility of CO_2 in blood and increasing the metabolic rate of the tissue and local CO_2 production (an increase of 4–5 % for every °C). Additionally, a final factor which accounts for the TC- CO_2 being higher than the $P_a\text{CO}_2$ is the local production of CO_2 from the epidermal cells of the skin. Therefore, to provide an accurate reflection of the $P_a\text{CO}_2$, the TC monitor must provide some type of temperature correction to account for these factors. The currently available TC monitors provide an internal temperature correction for the PCO_2 based on the working temperature of the electrode (Severinghaus 1982). At a working temperature of 43 °C, the conversion from $P_a\text{CO}_2$ to TC- CO_2 can be arrived at using the formula $\text{PCO}_2 = (\text{TC-}\text{CO}_2 \text{ divided by } 1.34) + 4 \text{ mmHg}$. Without temperature correction, there is an exaggeration of the normal TC to arterial

Fig. 12.12 Schematic representation of a transcutaneous O_2/CO_2 device. The heat produced by the sensor dilates the capillary bed thereby increasing local blood flow and facilitating the diffusion of O_2 and CO_2 from the capillary to the sensor. Transcutaneous O_2 and CO_2 are measured electrochemically in the sensor (Figure provided by Radiometer Inc.)



CO_2 gradient, which may lead one to question the validity and utility of such technology (Tremper et al. 1981).

The technology for TC blood gas monitoring was originally developed and described in the 1950s by two groups of investigators (Stow and Randall 1954; Severinghaus and Bradley 1958). TC- CO_2 value is determined by measuring changes in the pH of an electrolyte solution that is separated from the skin by a semipermeable membrane. Following the local application of heat from the surface of the monitoring electrode and the local vasodilatation of the capillary bed, CO_2 diffuses from the capillary lumen across the tissue planes and through the semipermeable membrane of the monitor. The movement of CO_2 into the electrolyte solution changes the pH of the solution. This change in pH is used to calculate the TC- CO_2 value.

Various types of TC- CO_2 monitors are currently available for clinical use. Those initially available for clinical use in the 1980s included the combination of both TC- O_2 and TC- CO_2 monitors. More recently, TC- CO_2 monitors are

available as a single TC- CO_2 electrode or as a combined pulse oximeter and TC- CO_2 monitor (Bendjelid et al. 2005; Dullenkopf et al. 2003; Tschupp and Fanconi 2003). The newer devices incorporate the two monitors into an earclip sensor which has found increased applications in the older pediatric and even the adult population. As with any type of monitoring technology, there are specific details of TC- CO_2 monitoring that are required to ensure its accuracy. In comparison to ET- CO_2 monitoring, TC- CO_2 equipment requires a longer preparation time including a calibration period, which varies from 1 to 3 min dependent on the manufacturer, prior to placement. This is followed by an additional 3–5 min equilibration period after placement of the electrode (Fig. 12.13) on the patient. This time is required to allow for heating of the skin to provide an equilibration between the TC and arterial CO_2 values. Additionally, with older generations of the TC- CO_2 monitor, removal of the electrode, recalibration, and placement at another site were recommended to avoid burning the skin. The TC- CO_2 electrode can be placed on any flat skin

Fig. 12.13 Transcutaneous CO₂ electrode with membrane in use on a patient



surface, or the newer electrodes can be clipped on an earlobe.

As the working temperature of the electrode is less (42 °C) with the newer generation of TC-CO₂ monitors, the need to reposition the electrode has decreased. However, frequent site changes are still suggested in preterm infants or other patient populations at risk for skin breakdown. Factors related to the monitor and electrode which may affect accuracy include technical variables such as trapped air bubbles under the electrode membrane, improper placement technique, damaged membranes, and inappropriate calibration techniques. Patient-related factors may also affect the accuracy of TC-CO₂ monitoring including skin thickness, the presence of edema, tissue hypoperfusion, or the administration of vasoconstricting drugs.

12.3.3 Clinical Applications of TC-CO₂ Monitoring

12.3.3.1 Neonatal Applications

The initial applications of TC blood gas monitoring (PCO₂ and PO₂) were in the neonatal ICU population, most importantly preterm infants with respiratory failure. Given the potential for oxygen toxicity and the development of retrolen-

tal fibroplasias as well as the risk of iatrogenic anemia related to repeated blood gas analysis, a device to provide a continuous readout of P_{O₂} was a welcome addition to the monitoring provided by pulse oximetry and intermittent blood gas monitoring. In the neonatal population, the correlation of the TC with arterial PCO₂ and PO₂ values is excellent given the thinner epidermis and the limited development of the stratum corneum in neonates compared to older infants and children. Continuous TC-O₂ monitoring in the neonatal periods allows a means of more effectively and accurately maintaining the desired level of oxygenation (P_aO₂ of 50–70 mmHg) as well as a means for the early identification of hypoxemia which may develop during routine care, handling, or invasive procedures. Routine screening with TC-O₂ monitors may also allow for the identification of significant respiratory or cardiac anomalies in otherwise asymptomatic neonates.

12.3.3.2 Monitoring During Mechanical Ventilation (Pediatric ICU)

Outside of the neonatal ICU population, one of the most frequent uses of TC-CO₂ monitoring is to provide a continuous monitor demonstrating the efficacy of ventilation during respiratory

failure in patients who require endotracheal intubation and ventilatory support. Various reports have demonstrated the accuracy of such monitoring in the PICU population (Tobias and Meyer 1997b; Berkenbosch et al. 2001; Tobias et al. 1999; Sivan et al. 1992). In two prospective comparisons involving PICU patients with respiratory failure requiring mechanical ventilation, TC-CO₂ was significantly closer to arterial PO₂ values than the simultaneously measured ET-CO₂ value (Tobias and Meyer 1997b; Berkenbosch et al. 2001). The efficacy of TC-CO₂ monitoring has also been demonstrated following cardiovascular surgery in infants and children with congenital heart disease (CHD) (Tobias et al. 1999). In all of these studies, various physiologic factors including increased dead space ventilation, residual shunt from CHD, and ventilation–perfusion mismatch can be expected to lead to significant inaccuracies with ET-CO₂ monitoring.

While the previously reviewed studies have used continuous TC-CO₂ monitoring, other investigators have evaluated its utility as an intermittent monitor of PCO₂. As a cost saving measure by avoiding the need to have a TC-CO₂ monitor at each bedside, Rauch et al. used intermittent TC-CO₂ monitoring in a PICU population of 19 patients ranging in age from 5 days to 16 years (Rauch et al. 1999). Prior to obtaining the $P_a\text{CO}_2$ sample, the TC-CO₂ device was applied and left in place for 5 min. The actual $P_a\text{CO}_2$ value varied from 19 to 86 mmHg. The mean difference between the TC and arterial CO₂ value was 1.94 mmHg with a 95 % confidence interval of –0.12–4.07 mmHg. Scatter plot analysis revealed a regression line characterized by the equation $P_a\text{CO}_2 = (\text{TC-CO}_2 \times 1.05) - 4.08$. Additional workup has demonstrated the utility and accuracy of TC-CO₂ monitoring during high-frequency oscillatory ventilation (Berkenbosch and Tobias 2002). Given the inability to use ET-CO₂ monitoring during high-frequency ventilation techniques, the authors demonstrated that TC-CO₂ monitoring can be used in this unique population of pediatric ICU patients. In the 100 paired values (TC and arterial CO₂) obtained from 14 patients ranging in age from 1 day to 16 years, the difference between the TC and arterial

CO₂ was 2.8 ± 1.9 mmHg. No difference in the accuracy of TC-CO₂ monitoring was noted when the arterial CO₂ was ≤ 50 mmHg versus when it was ≥ 50 mmHg. Given these results, TC-CO₂ monitoring is highly recommended during the use of HFOV.

12.3.3.3 Spontaneous Ventilation

Continuous monitoring of ventilatory function is equally important during spontaneous ventilation or assisted spontaneous ventilation with noninvasive ventilatory techniques. Continuous TC-CO₂ monitoring has been shown to provide evidence of previously unrecognized episodes of hypercarbia in adults during the immediate postoperative period or during the use of patient-controlled or epidural analgesia (Drummond et al. 1997; Kopka et al. 2007; McCormack et al. 2008). Additional reports suggest the utility of TC-CO₂ monitoring in spontaneously breathing pediatric patients with acute airway and respiratory events such as croup and status asthmaticus (Holmgren and Sixt 1992; Fanconi et al. 1991; Wennergren et al. 1986). Holmgren and Sixt evaluated the relationship between TC and arterial CO₂ in 14 children, 7–15 years of age, with status asthmaticus (Holmgren and Sixt 1992). The average TC-CO₂ value was 0.6 kPa (range, 0–1.5 kPa) higher than the $P_a\text{CO}_2$ (1 kPa = 7.3 mmHg). This relationship was not changed by the administration of β -adrenergic agents. In a cohort of 17 children with croup, a reduction in TC-CO₂ values and croup scores was noted following the administration of inhaled epinephrine (Fanconi et al. 1991). These changes were noted despite no change in other physiologic parameters including heart rate, oxygen saturation, or respiratory rate. The authors also noted a correlation of TC-CO₂ values with the croup scores and suggested that TC-CO₂ monitoring was a reliable and objective tool for managing patients with upper airway obstruction.

TC-CO₂ monitoring has also been used during the provision of noninvasive ventilation (NIV), another situation in which the accuracy of ET-CO₂ may be affected by the presence ventilation–perfusion mismatch due to parenchymal lung disease and sampling issues related to the

apparatus and mask. In a cohort of 26 adults receiving noninvasive ventilation, there was a good correlation ($r=0.968$) between TC and arterial CO_2 values over a $P_a\text{CO}_2$ range of 26–71 mmHg ($\text{TC}-\text{CO}_2=1.116\times P_a\text{CO}_2-0.46$) (Janseens et al. 1998; Storre et al. 2007). To date, only one study has investigated the use of TC- CO_2 monitoring during NIV in the pediatric population (Paiva et al. 2009). The study population included patient with acute respiratory problems supported with NIV and a second cohort of patients who were on long-term home NIV and required a sleep study evaluation. The first cohort included 65 patients with various respiratory issues including asthma, acute infectious problems, cystic fibrosis, interstitial lung disease, and neuromuscular disorders. Using linear regression analysis, the authors noted a clinically acceptable correlation of the TC and arterial CO_2 in all 3 age groups with $r=0.931$ in patients 0–6 years of age, $r=0.630$ in patients 7–12 years of age, and $r=0.505$ in patients 13–18 years of age. Bland–Altman analysis revealed that the TC- CO_2 value moderately underestimated the $P_a\text{CO}_2$ value with a mean bias of approximately 1 mmHg and a precision of approximately 4 mmHg. In the second cohort of patients, 21 of 50 patients were identified who manifested nocturnal hypercarbia ≥ 50 mmHg despite no evidence of hypoxemia and normal daytime blood gas measurements.

12.3.3.4 Intraoperative Applications

Although ETCO_2 monitoring remains an intraoperative standard of care to document the intratracheal presence of the ETT, various issues affecting ventilation–perfusion matching, the presence of shunt, and technical limitations may affect its accuracy in the operating room setting. When compared with the ICU setting, there are fewer studies reporting intraoperative applications of TC- CO_2 monitoring (McBride et al. 2002; Griffin et al. 2003; Bhavani-Shankar et al. 1998; Reid et al. 1992; Phan et al. 1987; Nosovitch et al. 2002). Nosovitch et al. demonstrated that TC- CO_2 monitoring was more accurate than ET monitoring during intraoperative care in a cohort of 30 pediatric patients (Nosovitch et al. 2002). The potential utility of TC- CO_2

monitoring was demonstrated by one of the patients who developed intraoperative bronchospasm. Despite an $\text{ET}-\text{CO}_2$ of 70 mmHg, the TC- CO_2 monitoring was reading 110 mmHg, while a simultaneous $P_a\text{CO}_2$ was 122 mmHg. Using the new combined ear sensor (TC- CO_2 and pulse oximetry), Dullenkopf et al. evaluated intraoperative TC- CO_2 monitoring in a cohort of 60 children receiving general anesthesia (Dullenkopf et al. 2003). Although there was no difference in the accuracy of ET versus TC- CO_2 monitoring in the general population, in a subset of patients with CHD, TC- CO_2 monitoring was more accurate (-0.039 ± 0.56 kPa versus 0.093 ± 0.64 kPa, $p<0.01$). Another scenario in which the anesthetic technique may impact on the accuracy of ETCO_2 is the use of one-lung ventilation (OLV) during thoracic surgical procedures. Four studies have demonstrated improved accuracy of TC compared to $\text{ET}-\text{CO}_2$ monitoring in this scenario (Ip Yam et al. 1994; Oshibuchi et al. 2003; Cox and Tobias 2007; Tobias 2003).

12.3.3.5 Apnea Testing

One component of the brain death examination is the demonstration of no ventilatory effort at a $P_a\text{CO}_2\geq 60$ mmHg. To accomplish, an apnea test is performed and an arterial blood gas is drawn to demonstrate a $P_a\text{CO}_2\geq 60$ mmHg. However, as the rate at which the $P_a\text{CO}_2$ increases is variable, it may be problematic to judge when the threshold $P_a\text{CO}_2$ of 60 mmHg has been achieved. Therefore, frequent ABGs are generally obtained to avoid waiting too long given the potential for hemodynamic compromise from hypercarbia or the development of hypoxemia. In both adult and pediatric patients, TC- CO_2 monitoring has been used to determine the appropriate time to obtain an ABG (Tobias 2001; Lang 1998). In a cohort of 8 pediatric patients, TC- CO_2 monitoring was employed during two separate apnea tests (Tobias 2001). In the first 2 patients of the cohort, the ABG was obtained when the TC- CO_2 was 60 mmHg. In all four instances, the $P_a\text{CO}_2$ was less than 60 mmHg. For the subsequent 6 patients, the ABG was drawn when the TC- CO_2 was ≥ 70 mmHg. In 11 of 12 apnea tests, the $P_a\text{CO}_2$ was greater than 60 mmHg, and in the other one,

the $P_a\text{CO}_2$ was 60 mmHg. In the 16 samples from the 8 patients, the TC to $P_a\text{CO}_2$ difference varied from 2 to 11 mmHg (5.8 ± 2.7 mmHg). If the ABG was obtained when the TC- CO_2 was ≥ 80 mmHg, the $P_a\text{CO}_2$ was ≥ 60 mmHg in all cases, and the TC to $P_a\text{CO}_2$ difference varied from 2 to 8 mmHg (5.4 ± 1.9 mmHg).

12.3.3.6 Monitoring of Acid–Base Status

Given the relationship between $P_a\text{CO}_2$, pH, and serum bicarbonate, TC- CO_2 may also have clinical utility as a means of evaluating changes in pH during pathologic processes that result in metabolic acidosis. During diabetic ketoacidosis (DKA), acidosis is partially compensated by a decrease in the $P_a\text{CO}_2$ related to an increase in minute ventilation. With appropriate therapy and resolution of the metabolic acidosis, the $P_a\text{CO}_2$ returns to normal values. In a cohort of 30 children with DKA, it has been demonstrated that TC- CO_2 monitoring can be used to follow changes in pH during treatment and resolution of the metabolic acidosis (McBride et al. 2004). In 2 of the patients, TC- CO_2 monitoring was not feasible due to poor tissue perfusion. In the remaining 28 patients, there was a gradual increase in the TC- CO_2 during correction of metabolic acidosis. Using the equation $P_a\text{CO}_2 = (1.5 \times \text{serum bicarbonate}) + 8$, a calculated bicarbonate value was determined and compared to simultaneously obtained serum bicarbonate values. The difference between the calculated and actual serum bicarbonate values was 1.5 ± 1.2 mmol/L. The difference was ≤ 2 mmol/L in 74.4 % of the sample sets and ≤ 5 mmol/L in 99.2 % of the sample sets. Linear regression analysis of calculated versus actual serum bicarbonate revealed a slope of 0.95 and an r (Johns et al. 1969) value of 0.88. From this linear regression analysis, the authors suggested that the serum bicarbonate could be calculated from the TC- CO_2 value by using the equation $\text{serum bicarbonate} = 0.61 \times (\text{TC-}\text{CO}_2 - 3.9)$.

12.3.3.7 Evaluation of Tissue Perfusion

As noted previously, the accuracy of TC- CO_2 monitoring is affected by tissue perfusion. In the

previously mentioned study evaluating the correlation of TC and arterial CO_2 in patients with CHD following cardiovascular surgery, it was noted that TC- CO_2 monitoring could not be used in patients receiving high doses of inotropic agents that resulted in peripheral vasoconstriction and/or in those with poor peripheral perfusion (Tobias et al. 1999). The impact of hemodynamic instability with poor tissue perfusion on TC- CO_2 monitoring has also been reported in a group of adult patients from a mixed operating room and ICU setting (Tremper et al. 1981). When the cardiac index was ≤ 1.5 L/min/m², there was an increase in the TC to arterial CO_2 gradient. The TC- CO_2 value trended inversely with the cardiac index rather than the $P_a\text{CO}_2$. Given this relationship, other investigators have suggested the utility of measuring TC- CO_2 as a means of evaluating tissue perfusion (Greenhalgh and Warden 1992; Tatevossian et al. 2000; Tobias et al. 2006). Greenhalgh and Warden applied intermittent TC CO_2 and O_2 monitoring on the day of surgery and then daily for the next 2 weeks following partial-thickness skin grafts for burn injury in 13 adults (Greenhalgh and Warden 1992). The TC- CO_2 values from the grafts were 80–100 mmHg for the initial few days and then decreased to levels that were slightly higher than those of normal skin (40–50 mmHg) by day 5–6 after grafting. The authors suggested that graft TC- CO_2 levels can be used to provide a noninvasive and objective measure of skin graft vascularization. Other authors have used TC- CO_2 and O_2 values as a means of evaluating peripheral perfusion during resuscitation (Tatevossian et al. 2000). When compared with survivors, non-survivors had lower TC- O_2 and higher TC- CO_2 values. All patients who maintained a TC- $\text{O}_2 \geq 150$ mmHg survived. A TC- $\text{O}_2 \leq 50$ mmHg for ≥ 60 min or a TC- $\text{CO}_2 \geq 60$ mmHg for ≥ 30 min was associated with a 90 % mortality.

TC- CO_2 monitoring has also been used to evaluate changes in tissue PCO_2 during aortic cross-clamping for repair of aortic coarctation (Tobias et al. 2006). The study protocol included TC- CO_2 monitoring from a site above the aortic cross-clamp (right chest wall) and a site below

(right thigh). Following placement of the aortic cross-clamp, there was a progressive rise in the tissue CO₂ (TC-CO₂) below the region of the cross-clamp (right thigh), while no change was noted above the cross-clamp. TC-CO₂ increased from 41 ± 4 to 92 ± 41 mmHg during the period of aortic cross-clamping which varied from 12 to 20 min. There was significant variability in the increase of the TC-CO₂ below the cross-clamp (4–127 mmHg), which the authors speculated resulted from the variability of the collateral circulation around the aortic coarctation. There was a correlation between the TC-CO₂ increase and the age of the patient with less of an increase in older patients who likely had time to develop collaterals. The authors suggested that TC-CO₂ monitoring might be able to predict extreme degrees of tissue hypoperfusion distal to the cross-clamp and might therefore be able to identify patients at risk for spinal cord ischemia.

12.3.4 Summary

Although still used most commonly in the neonatal period, an improved understanding of the techniques of TC-CO₂ monitoring and the availability of new monitors have led to the increased use of TC-CO₂ monitoring in various clinical scenarios outside of the neonatal population. Despite specific limitations of the technology (Table 12.8), when compared with ET-CO₂ monitoring, TC-CO₂ monitoring is equally as accurate in patients with normal respiratory function and more accurate in patients with shunt or ventilation–perfusion inequalities. Additionally, TC-CO₂ monitoring can be applied in situations that may preclude ET-CO₂ monitoring such as HFOV, apnea testing, and NIV. TC-CO₂ monitoring has been used in spontaneously breathing patients with airway and respiratory issues (croup and status asthmaticus) as well as a means of monitoring metabolic status during treatment of acidosis related to DKA. TC-CO₂ monitoring should not be used to replace ET-CO₂ monitoring as ET-CO₂ monitoring remains the standard of care to demonstrate the intratracheal location of the ETT following endotracheal intubation and

Table 12.8 Potential limitations of TC-CO₂ monitoring

More labor intensive for respiratory therapy staff
Device requires calibration and setup time
Lag time between change in arterial oxygen and TC oxygen
Depending on type of device used, may require calibration and site change at specific intervals
Accuracy affected by specific patient factors including: - Low perfusion states - Administration of inotropic agents with vasoconstricting properties - Tissue edema or subcutaneous fat
Potential for superficial burns and blistering especially in preterm infants
Limited, but increasing clinical experience outside of neonatal population
Limited clinician familiarity with its use
Device must have intrinsic calibration to eliminate discrepancy due to increased tissue metabolism and CO ₂ production from heat.

as a disconnect alarm in the operating room. Given the complementary nature of these two noninvasive monitors, their combined use should be considered in critically ill pediatric patients in both the pediatric ICU and the operating room settings.

Essentials to Remember

- TC-CO₂ monitors apply heat (42–43 °C) to the skin to induce vasodilatation of the capillary bed which results in the equilibration of capillary and arterial PCO₂ levels.
- Although used most commonly in neonates, improvement in the technology of TC-CO₂ monitoring has led to the increased use of TC-CO₂ monitoring in various clinical scenarios outside of the neonatal population.
- Despite limitations of the technology, when compared with ET-CO₂ monitoring, TC-CO₂ monitoring is equally as accurate in patients with normal respiratory function and more accurate in patients with shunt or ventilation–perfusion inequalities.

- TC-CO₂ monitoring can be applied in situations that may preclude ET-CO₂ monitoring such as HFOV, apnea testing, and NIV and in spontaneously breathing patients with airway and respiratory issues (croup and status asthmaticus). It can also be used to evaluate metabolic status during treatment of acidosis related to DKA.
- TC-CO₂ monitoring should not be used to replace ET-CO₂ monitoring as ET-CO₂ monitoring remains the standard of care to demonstrate the intratracheal location of the ETT following endotracheal intubation and as a disconnect alarm in the operating room. Given the complementary nature of these two noninvasive monitors, their combined use should be considered in critically ill pediatric patients in both the pediatric ICU and the operating room settings.

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Monitoring of the Mechanical Behaviour of the Respiratory System During Controlled Mechanical Ventilation

13

Most modern mechanical ventilators offer a multitude of graphics and numerics allowing to monitor respiratory mechanics during ongoing mechanical ventilation. The information provided by these integrated respiration monitors is first to provide the information necessary to optimise ventilator settings in an individual patient and second to document disease evolution over time or in response to therapeutic interventions. Furthermore, measuring respiratory mechanics during ventilation can allow developing automatic adaptation algorithms of ventilator settings. However, to do this either by manual or by automatic ventilator settings adjustment, a thorough understanding not only of basic respiratory mechanics during mechanical ventilation is needed but also a good understanding what graphs and numbers can tell the physician or respiratory therapist at bedside. Graphic monitoring shows graphs generated from the signals of airway pressure (as usually measured at the airway opening, e.g. endotracheal tube or face mask connection), gas flow and volume change of the respiratory system. Volume is in fact measured by the time-integral of gas flow. It must be noted also that all the measurements derived from the airway opening pressure include the resistance of the artificial airway (i.e. endotracheal tube) as part of the respiratory system resistance.

Classically the following curves and loops can be displayed: pressure, flow or volume over time, pressure–volume (as an indicator of dynamic

compliance), pressure–flow (as an indicator of resistance) and flow volume.

13.1 Respiratory System Compliance (i.e. The Pressure–Volume Relationship) During Ongoing Mechanical Ventilation

Peter C. Rimensberger and David Tingay

Educational Aims

- To understand what information can be gathered from respiratory system compliance measurements
- To review various factors and error sources that might influence dynamic compliance measurements during ongoing mechanical ventilation
- To understand why analysis of the shape of the dynamic *PV* curve can give more helpful information than analysis of respiratory system compliance values only
- To understand the difficulties and limited value of respiratory compliance measurements during high-frequency ventilation (HFV)

During mechanical ventilation, respiratory mechanics can be assessed by studying the pressure–volume (*PV*) relationship, describing the elastic properties of the respiratory system, lungs and chest wall, above end-expiratory lung volume (EELV) or functional residual capacity (FRC). However, it is apparent that a complete description of the elastic behaviour of the respiratory system would require measurements made over the complete volume range, from residual volume (RV) to total lung capacity (TLC).

Analysis of the *PV* relationship can be used in two ways, first to describe the overall compliance of the respiratory system under quasi-static conditions, which might be used as an indicator of evolution of lung disease over time, and second for setting ventilator pressures within the range that is thought to be safe (i.e. above the lower (LIP) and below the upper inflection point (UIP) (for further information see Sect. 11.8). The segment between the LIP and the UIP represents a zone of best compliance within tidal ventilation should occur (Fig. 13.1). However, it has been realised that the real *PV* curve of the respiratory system, which describes respiratory system behaviour, has to be obtained during static or at least semi-static conditions (i.e. no flow conditions or low flow conditions, respectively) to avoid artefacts mainly due to various forces opposing inspiratory flow such as:

- Viscous forces (friction along the endotracheal tube, the airways and lung tissue affecting flow)
- Elastic forces (elastic forces by the lung and elastic recoil forces by the chest wall)
- Viscoelastic forces (stress adaptation within lung and chest wall tissues)
- Inertial forces (at the start of inspiration and expiration)

Additional factors that will induce additional errors in *PV* measurements are:

- Compressibility of gases
- Gas resorption in the lungs

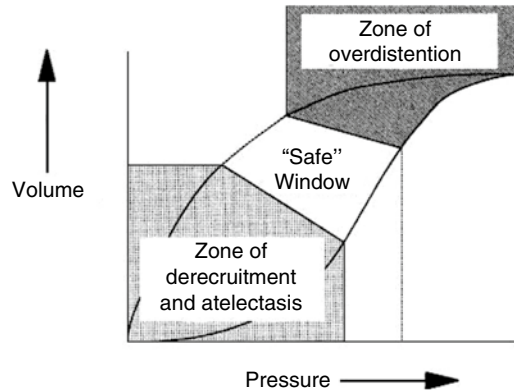


Fig. 13.1 Pressure–volume curve of a moderately diseased lung, such as one with adult respiratory distress syndrome. Two hazard zones exist. In the zone of overdistention, damage occurs from oedema fluid accumulation, surfactant degradation, high oxygen exposure and mechanical disruption. In the zone of derecruitment and atelectasis, lung injury develops through the direct trauma of repeated closure and reexpansion of airways and alveoli, by stimulation of the lung’s inflammatory response, by inhibition of surfactant, through the effects of local hypoxemia, and through compensatory overexpansion of the rest of the lungs as the lung ‘shrinks’. High end-expiratory pressures and small tidal volumes are needed to stay in the ‘safe’ window (Reprinted with permission from Froese (1997))

- Inertial forces (at the beginning of both, inspiration and expiration)
- Inhomogeneity within the lungs with inhomogeneous filling behaviour of various lung regions

Generation of the static or semi-static *PV* curve on bedside is cumbersome using either step-by-step or occlusion inflation/deflation methods, alternatively continuous slow flow inflation methods have been proposed (Sydow et al. 1991, 1993; D’Angelo et al. 1994; Ranieri et al. 1994; Lu et al. 1999). All methods require the patient being sedated and muscle paralysed. The advantage of this static and semi-static measurements is, because of pressure and volume readings, made under no flow conditions and in steady state condition of the system (i.e. only when a stable pressure reading is reached) for the

step-by-step inflation and deflation method by a super-syringe using small volume aliquots or during no flow for the flow interruption techniques during constant low flow inflation (Lu et al. 1999) that airway resistance does not, or almost not, influence measurements of the respiratory systems *PV* curve that describes the behaviour of the respiratory system over the whole volume range, i.e. from functional residual capacity to total lung capacity.

In cooperative subjects, it is possible to measure the *PV* curve starting at RV, which influences the shape of the inflation, but not of the deflation, *PV* curves. Likewise, in an excised lung, *PV* curves can be obtained from the degassed state, and this has a profound effect on the shape of the inflation limb of the *PV* curve, while the deflation limb remains unchanged. In other words, the shape of the inflation limb depends on the initial lung volume at which its determination starts (Jonson et al. 1999). However, making measurements from RV is impractical and indeed dangerous in patients with acute lung injury. Therefore, measurements of *PV* curves are generally made starting from end-expiratory lung volume (EELV) at 0 cm H₂O airway pressure. In normal subjects, EELV is synonymous with FRC, defined as the volume determined by the balance of static passive forces of the lung and chest wall (see Fig. 11.23, Sect. 11.8).

By definition, positive pressure ventilation with a PEEP value above 0 cm H₂O in a sedated and paralysed patient occurs above FRC. Therefore, with any setting on the ventilator, only the volume above the FRC can be modified according to the characteristics of the *PV* curve (i.e. compliance and hysteresis). In some patients the FRC is virtually at the RV; in others there is a substantial expiratory reserve volume. If the disease is associated with a highly compliant lung or chest wall, the FRC will be high, and, conversely, if the lung or chest wall compliance is low, the FRC will be low. In the former case, one may not see an inflection point on the inflation limb of the *PV* curve, whereas it will probably be present

in the latter. The position of the FRC within the TLC is thus ‘disease specific’ and the problem is that even when FRC is measured with a gas dilution technique, it is difficult to assess it in relation to the TLC. Furthermore, in ALI/ARDS there is a significant portion of the intrathoracic gas volume occupied by tissue oedema, fluids and inflammatory cells, as evidenced by computed tomographic studies; therefore lung gas volume measurements may not always be predictive of total thoracic volume (Gattinoni et al. 1998). A further difficulty is that if by some ventilatory strategy, although one succeeds in increasing lung volume, one is never sure whether this is due to recruiting new gas exchange units (good) or overdistending already open units (bad) (Rouby et al. 2002).

Furthermore, for the purpose of such measurements, it would be necessary to interrupt the normal ventilatory pattern of the patient, which does require the patient to be passive, which often means to be paralysed (for further information see Sect. 11.8).

13.1.1 Dynamic Pressure–Volume–Loop Analysis and Dynamic Compliance for Assessment of Disease Evolution

Static or semi-static methods of *PV* measurements may offer a diagnostic tool (Bone 1976) diagnosis of causes for acute respiratory distress syndrome (i.e. extrapulmonary versus intrapulmonary ARDS) allowing to describe progress of disease (Falke et al. 1972; Suter et al. 1975; Matamis et al. 1984) or document the effect of treatment or an intervention (Lachmann et al. 1982; Tooley et al. 1987) (Pfenninger et al. 1992); the latter can be of special interest for various clinical research purposes and eventually allow for prognosis (Gattinoni et al. 1984), but they cannot be used for continuous monitoring of respiratory mechanics during ongoing ventilation.

13.1.2 Dynamic Pressure–Volume–Loop Analysis and Dynamic Compliance Measurements for Choosing Ventilator Settings

13.1.2.1 During Conventional Ventilation

There exists a certain interest in using measurements and analysis of respiratory mechanics during ongoing mechanical ventilation that could help to improve ventilator settings. However, mechanical properties of the respiratory system assessed under the dynamic condition of mechanical ventilation are not equivalent to those assessed under static conditions (Stahl et al. 2006). The observations that (1) the inflation limb of the quasi-static *PV* curve (as generated by the supersyringe or low flow inflation methods) is distinctly different from the deflation limb, (2) the inflation limb is highly sensitive to the initial inflation conditions (i.e. whether inflation starts from zero PEEP or another PEEP level) (Jonson et al. 1999) and preceding lung history (i.e. whether the patient was disconnected or even suctioned shortly before), and (3) the tidal cycle is not placed on the inflation limb of the quasi-static *PV* (Rimensberger et al. 1999) illustrate well how difficult it can be to use the slope of the tidal cycle *PV* curve (i.e. dynamic compliance) during titration of PEEP stepwise upwards as only indicator for best ventilator settings as suggested many years ago (Suter et al. 1975, 1978). The following strategies might potentially help, despite several limitations of each method, to optimise PEEP and V_t or plateau or peak pressure setting, respectively.

13.1.2.1.1 Optimising PEEP by Dynamic Compliance Measurements and Graphic Analysis

- Classically, as cited in several textbooks, it has been thought that changes in dynamic compliance values during upward titration of PEEP would clearly indicate the best PEEP level given the concept that the tidal cycle would move along the static inflation *PV* curve of the

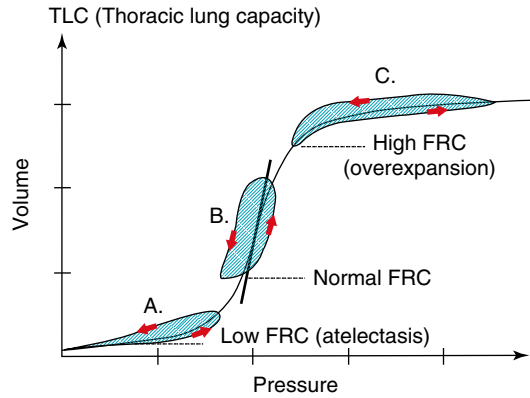


Fig. 13.2 Classically, as cited in several textbooks and company handbooks, it has been thought that changes in dynamic compliance (indicated by the slope of the ventilatory *PV*-cycle in green color) would clearly indicate the best PEEP level (in this example scenario B) given the concept that the tidal cycle would move along the static inflation *PV*-curve of the respiratory system. This does not take in account hysteresis of the respiratory system and is therefore over simplified. The ventilatory tidal cycle never lies on the inflation limb of the static *PV*-curve (see also Fig. 13.3)

respiratory system (Fig. 13.2). With the recognition that *PV* hysteresis of the respiratory system exists (Escolar et al. 2002; Escolar and Escolar 2004) (see also Sect. 11.8), that the deflation limb of the static *PV* is much more stable and therefore relatively independent from lung history (i.e. previous inflation conditions) (Rimensberger and Bryan 1999) and that after a lung recruitment the dynamic *PV* cycle during ongoing ventilation can be placed on the deflation limb of the corresponding static *PV* curve (Fig. 13.3), it has been suggested to use a decremental PEEP following a recruitment manoeuvre to identify optimal PEEP settings (Rimensberger and Bryan 1999; Hickling 2001; Suarez-Sipmann et al. 2007; Maisch et al. 2008). The PEEP that resulted in the highest compliance during decremental PEEP steps is considered to be optimal (Fig. 13.4). Furthermore, it has been shown that changes in aerated and non-aerated lung volumes induced by a lung recruitment manoeuvre can be adequately represented by respiratory compliance but much less by

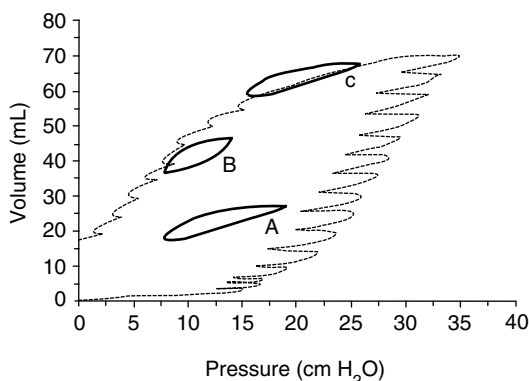


Fig. 13.3 Dynamic loops (tidal volume, 5 mL/kg) with 3 PEEP settings with and w/o lung recruitment inscribed into the quasi-static pressure/volume curve of the respiratory system of one animal after surfactant depletion with repeated lung washes: (A) $PEEP < P_{inf}$ without preceding SI; (B) $PEEP < P_{inf}$ after a SI; (C) $PEEP > P_{inf}$. Note that the dynamic loop A ($PEEP$ without any sustained inflation) is positioned above the inflation limb of the static PV curve and that loop B ($PEEP$ after sustained inflation) is positioned on the deflation limb of the static PV curve. With $PEEP > P_{inf}$, the dynamic loop (C) is on the asymptote of the static PV curve. $PEEP$ positive end-expiratory pressure, P_{inf} lower inflection point on the inflation limb of the overall PV curve, SI sustained inflation (Reprinted with permission from Rimensberger et al. (1999))

changes in oxygenation or shunt (Henzler et al. 2005). This approach of using the individual patient's lung mechanics to open the lung and set PEEP is very promising because of its ease for implementation (Hermle et al. 2002).

- Alternatively, the lower and upper inflection points of the quasi-static PV curve were regarded repeatedly as points of interest to avoid cyclic derecruitment and overdistension and to optimise ventilatory settings (Fig. 13.5). However, this concept is not fully appropriate since it has been clearly shown that alveolar reinflation occurs along the whole P/V curve. In addition, the dynamic tidal cycle is positioned always above the inflation limb of the quasi-static PV curve (Rimensberger et al. 1999; Hickling 2001) (Figs. 13.6 and 13.7), and this is more marked when PV hysteresis is important. Therefore, the lower inflection point has no relationship with alveolar opening and closure and does not indicate the positive end-expiratory pressure needed to prevent alveolar collapse (Maggiore et al. 2003). In short, identification of a lower inflection point on the dynamic pressure–volume loops

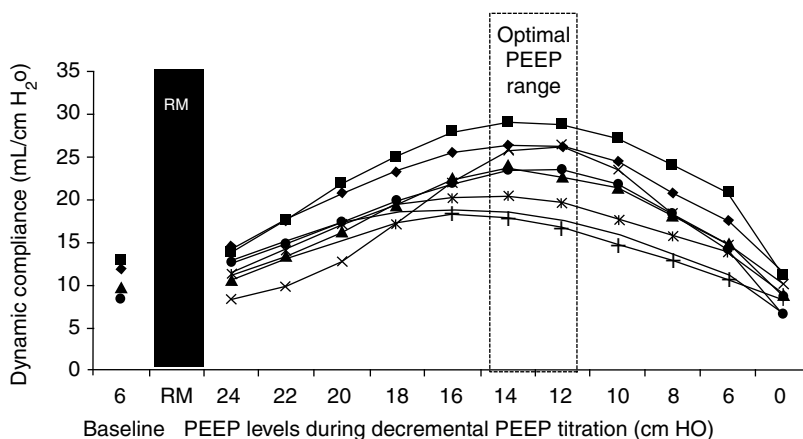


Fig. 13.4 Individual changes in dynamic compliance decremental PEEP steps after a recruitment manoeuvre (RM) in an experimental study. A biphasic response (i.e. a first increment and a subsequent decrement with a visually identifiable maximum) can be observed. Each

symbol represents an individual animal. RM recruitment manoeuvre, $PEEP$ positive end-expiratory pressure (Modified with permission from Suarez-Sipmann et al. (2007))

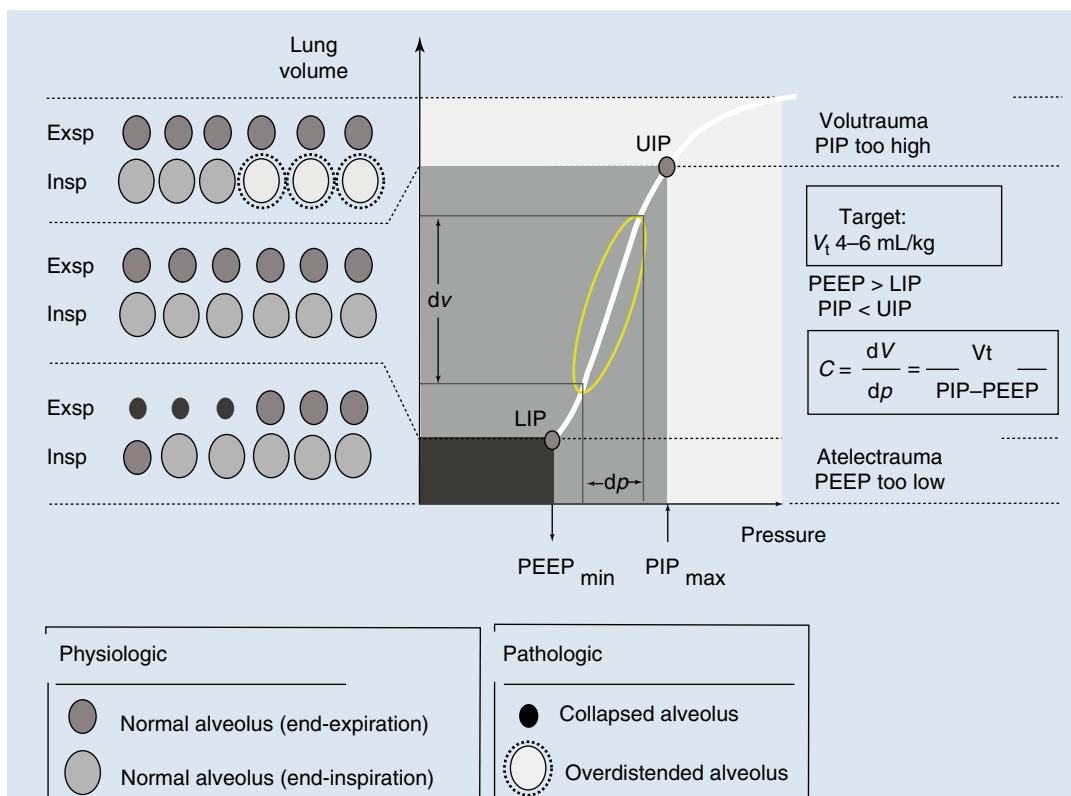
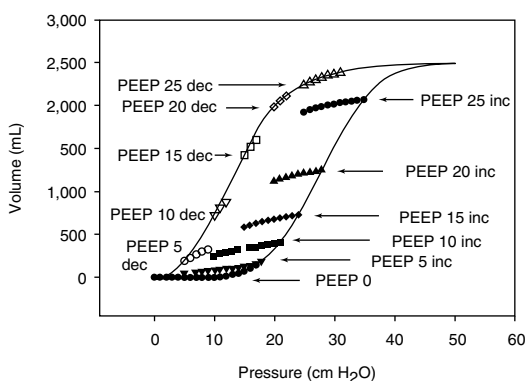


Fig. 13.5 The classical concept of the interpretation of the pressure–volume curve indicates that with positioning the tidal cycle by using a PEEP value above the lower inflection point (*LIP*), the risk for atelectrauma should be reduced, and with positioning the tidal cycle by using a *PIP* value below the upper inflection point (*UIP*), the risk

for volutrauma should be reduced. *PEEP* positive end-expiratory pressure, *PIP* positive inspiratory pressure, *LIP* lower inflection point, *UIP* upper inflection point, *C* compliance, *dV* delta volume = tidal volume, *dp* delta pressure, *V_t* tidal volume (With permission, modified from Berger and Stocker (2004))

Fig. 13.6 Inspiratory tidal *PV* plots with *V_T* 140 ml with incremental (black symbols) and decremental (open symbols) PEEP levels from 0 to 25 cm H₂O derived mathematically from multiple units lung model. At each PEEP level, the volume at equivalent pressures and the mean tidal *PV* slope (i.e. tidal cycle compliance or dynamic compliance during conventional mechanical ventilation) are greater during decremental PEEP. With zero PEEP, the plots for incremental and decremental PEEP are superimposed. Note that the dynamic tidal *PV* cycle is never positioned on the plotted inflation limb of the overall *PV* curve (Reprinted with permission from Hickling (2001))



obtained during tidal ventilation should *not be used* to guide PEEP settings (Adams et al. 2001) (see also Sect. 11.8.2).

- However, airway graphics can, despite the limitations mentioned above, be useful to guide ventilation.

1. One possible strategy is to use airway graphics to determine ‘best’ PEEP (Fig. 13.8) in order to avoid airway collapse end-expiration, as testified by a flat horizontal dynamic pressure–volume (*PV*) curve (0 volume reading between the set PEEP and

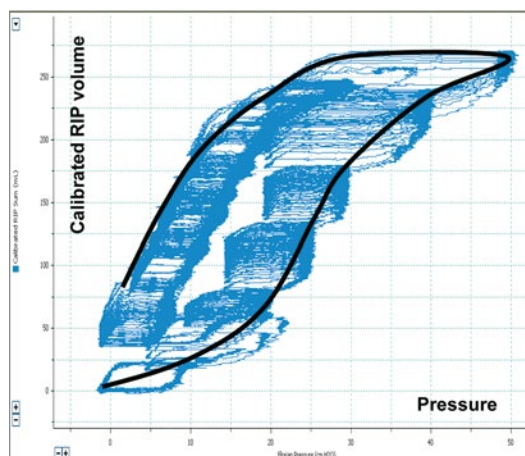


Fig. 13.7 Tracing of the dynamic pressure–volume curve (blue line) during incremental and decremental PEEP steps using volume-calibrated respiratory inductive plethysmography (RIP) in an animal after surfactant depletion by repeated lung washes and superimposed the theoretical quasi-static PV curve (black line). Note that the lower inflection point on the static PV curve (i.e. PV envelop) has no relationship with alveolar opening and closure and does not indicate directly the positive end-expiratory pressure needed to open the lung or to prevent alveolar collapse

a higher pressure level at which airway opening will start to happen). Whereas when the first part of the PV curve from set PEEP shows a slow and a second part a fast increase in volume (Fig. 13.8), this will not indicate that PEEP settings are too low and therefore allowing for collapse. Such a phenomenon is a result of initial fast flows in a high resistive system (endotracheal tube) during rapid increase of airway pressures, because pressures are measured in the respiratory circuit at the ETT connection (i.e. before the part of high resistance in the respiratory circuit that includes the endotracheal tube) and not on the tracheal level (Karason et al. 2000) (see Fig. 11.27). Therefore, the dynamic PV loop *cannot* give a clear indication on the required PEEP level. However, a completely flat and horizontal line for the first part of the inflation limb might suggest that there might be no volume change induced when pressures are increased which could indicate that there is major lung collapse during the first part of lung inflation. Whereas

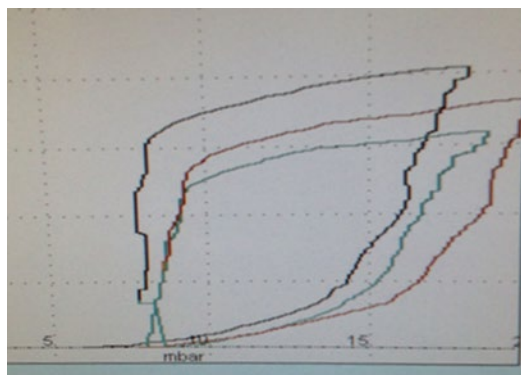


Fig. 13.8 Dynamic pressure loop as displayed by the SLE 5000 ventilator in the TCPL mode. PEEP and PIP are increased from 6 to 8 and PIP from 18 to 20 cm H₂O within three breath cycles. Note the shift of the lower inflection point (LIP) from 14 cm H₂O with a PEEP setting of 6 cm H₂O (black line) to 16.5 cm H₂O with a PEEP setting of 8 cm H₂O (red line). The green line depicts the respiratory cycle occurring during changes of settings are made. The appearance of a LIP is a result of airway resistance during fast flow inflation and does not indicate lung opening. TCPL Time cycled pressure limited

when the first part of the PV curve from set PEEP shows a slow and a second part a fast increase in volume. The change in curvature of the inflation limb is related mainly to endotracheal tube resistance. This latter does not indicate that PEEP settings are too low. This can be easily confirmed by the observation that this ‘lower inflection point’ is shifted to the right when PEEP is increased (Fig. 13.8, see also Fig. 11.27 in Sect. 11.8).

2. On the other side of the PV range, pulmonary overdistension occurs when the volume limit of some areas of the lungs is approached. It will be manifested as a dramatic reduction in compliance at the terminal end of the breath. This commonly is referred to as ‘beaking’ and often numerically expressed as by the C20/C value (i.e. the ratio between the slope, i.e. compliance of the last 20 % of the upper pressure range and the slope, i.e. compliance of the total PV loop) (see Fig. 11.51). Overdistension should be avoided as it has several deleterious effects on the cardiovascular and pulmonary system. First, overdistension puts the patient at risk for baro-/volutrauma.

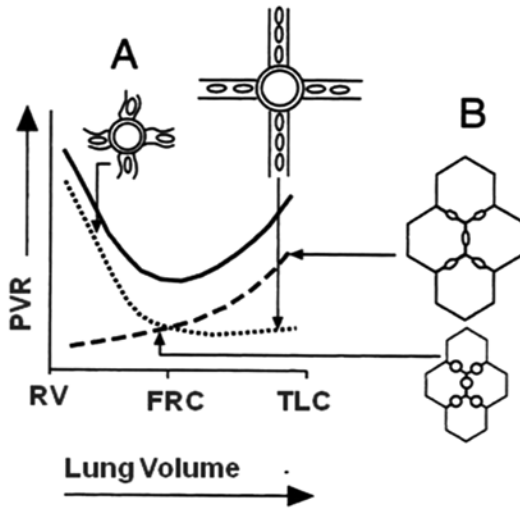


Fig. 13.9 Pulmonary vascular resistance (PVR) is lowest at functional residual capacity (FRC). In the diseased lung, FRC is in general reduced due to lung infiltration, consolidation, atelectasis or presence of interstitial oedema, with resultant loss of pulmonary vascular integrity and increased PVR (A). Any recruitment in lung volumes in order to restore as much as possible normal FRC will therefore lower PVR, whereas overdistension of lung units will again increase PVR through compression of the pulmonary vascular bed (B)

Second, overdistension can increase dead space and therefore render ventilation less efficient. Third, overdistension will result in a dramatic increase in pulmonary vascular resistance (Fig. 13.9) from pulmonary vascular compression and a resultant reduction in cardiac output. These effects will be even more dramatic at higher levels of PEEP while maintaining identical V_t or driving pressure ($\Delta P = PIP - PEEP$). When terminal ‘beaking’ is observed, the clinician should reduce the set PIP or V_t to reduce the risk of overdistension of some lung areas.

3. A third concept would be the analysis of the curvature of the pressure–time curve generated during a low flow inflation for V_t delivery. Ranieri et al. have shown that this might allow to detect variations in compliance during tidal inflation, indicating either the occurrence of alveolar overdistension at end-inspiration, or alveolar recruitment during tidal inflation (Figs. 13.10 and 13.11) (Ranieri et al. 2000). Hammer and

colleagues measured FRC in relation to TLC by gas dilution in children with a variety of lung disease. Determination of TLC and FRC (i.e. the FRC/TLC ratio) allowed estimating the degree of lung overinflation (Hammer et al. 1998). However, for bedside application this latter method is not as simple to be used.

13.1.2.1.2 Identification of Dynamic Hyperexpansion

When airway resistance is high and/or fast respiratory rates are used, the patient is at risk for dynamic hyperexpansion. This occurs when exhalation does not come to completion. As a result there is retained gas in the patient’s respiratory system (i.e. ‘gas trapping’) leading to intrinsic PEEP, which is difficult to control and should be if any possible avoided. Dynamic hyperexpansion might decrease venous return and hence preload and cardiac output. To limit the risk for dynamic hyperexpansion, one should decrease the T_i , which if becoming inappropriately short may decrease delivered V_t (see above) or reduce the ventilatory rate to allow for a longer T_E .

13.1.2.2 During High-Frequency Ventilation

13.1.2.2.1 Monitoring of Compliance During High-Frequency Ventilation

There is substantial animal evidence to suggest that static compliance (Cr_s) can be used to determine the optimal application of high-frequency ventilation (HFV). Byford et al. (1988) showed that improvements in static and ‘quasi-static’ Cr_s were directly related to the magnitude of mean airway pressure (P_{aw}) change, and subsequent recruitment achieved, after sustained inflations during HFV in surfactant-deficient rabbits. Later, Bond and Froese (1993) also reported, in the same animal model, an improvement in Cr_s after application of a volume recruitment manoeuvre during HFV. The deflation limb of the pressure–volume relationship has been repeatedly shown to coincide with the point of optimal static Cr_s during HFV (Rimensberger et al. 1999, 2000a; Goddon et al. 2001; McCulloch et al. 1988; Pillow et al. 2004). Finally, Wood et al.

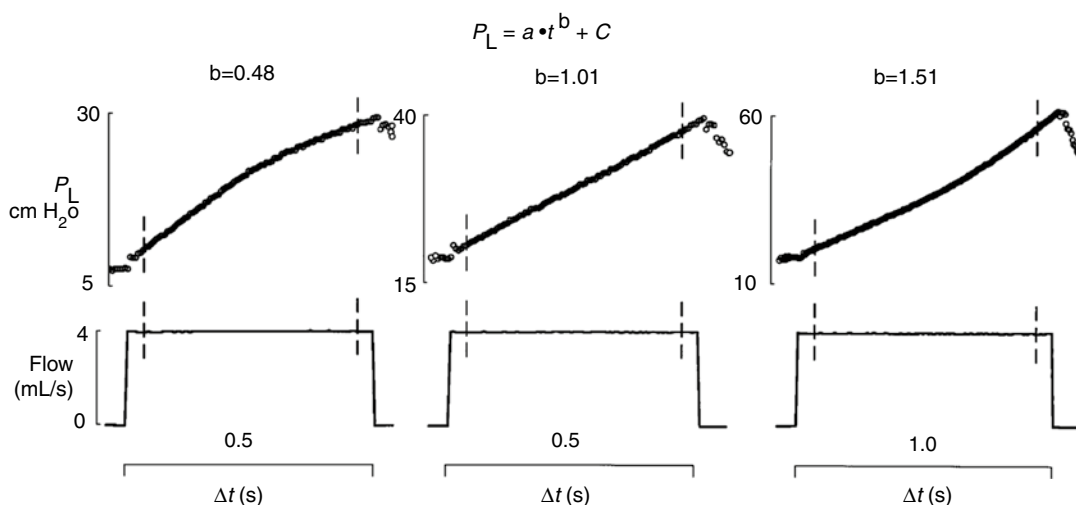


Fig. 13.10 The conceptual illustration of the dynamic pressure–time (P – t) curve. Based on the power equation $P_L = a \cdot t^b + c$, $b=0.5$ produces a convex P – t curve, indicating continuing recruitment; $b=1$ produces a straight P – t line, indicating no alveolar continuing recruitment or

overdistension; and $b=1.5$ produces a concave P – t curve, indicating alveolar overdistension. The power equation was applied to the transpulmonary pressure (PL) signal during a constant inspiratory flow (vertical bars) (Reprinted with permission from Ranieri et al. (2000))

(2002) were able to identify atelectasis and overdistension on the inflation limb using static Crs. Monitoring of static Crs in patients receiving HFV is difficult as it requires cessation removal from tidal ventilation. Monitoring of dynamic Crs is problematic during HFV. The reasons for this are outlined below.

13.1.2.2.2 Difficulties in Determining Dynamic Crs During High-Frequency Ventilation

Despite the potential benefits of understanding the mechanical properties of the respiratory system during high-frequency ventilation, direct monitoring of dynamic Crs and resistance (R_{RS}) is rarely performed at the bedside. This is due to the difficulties in determining both parameters during HFV. HFV is characterised by high flow, low tidal volume, low intra-alveolar change in pressure and high rate conditions, a situation that limits measurement conditions due to lower signal to noise ratio. It is worth considering the other reasons that limit monitoring of dynamic Crs during HFV.

13.1.2.2.3 Wave Form Attenuation

Unlike conventional modes of ventilation, change in pressure at the airway opening (ΔP) cannot be considered equal to change in transpulmonary

pressure (P_{TP}) during HFV (Gerstmann et al. 1990). Attenuation of waveform characteristics is not constant and influenced by multiple factors, including the resistance in the endotracheal tube and lung mechanics of the airways, lung tissue and chest wall (Pillow et al. 2002). Increasing alveolar compliance reduced the attenuation while increasing chest wall resistance increased it. Most modern HFV are limited to the measurement of airway pressure and flow at the airway opening; during HFV these measurements can only be considered proxies of the intrapulmonary mechanics.

13.1.2.2.4 Mathematical Assumptions of Respiratory System Mechanics

All commonly applied bedside methods of determining Crs, and R_{RS} (see also Sects. 11.8 and 13.2) during mechanical ventilation apply mathematical assumptions to model the complex mechanical behaviour of the respiratory system. These assumptions are generally not valid during HFV or require computations beyond the capacity of most modern ventilators.

Although the *Mead-Whittenberger analysis* (Mead and Whittenberger 1953) is an accepted method of calculating Crs during mechanical ventilation, it cannot be applied to HFV, given the

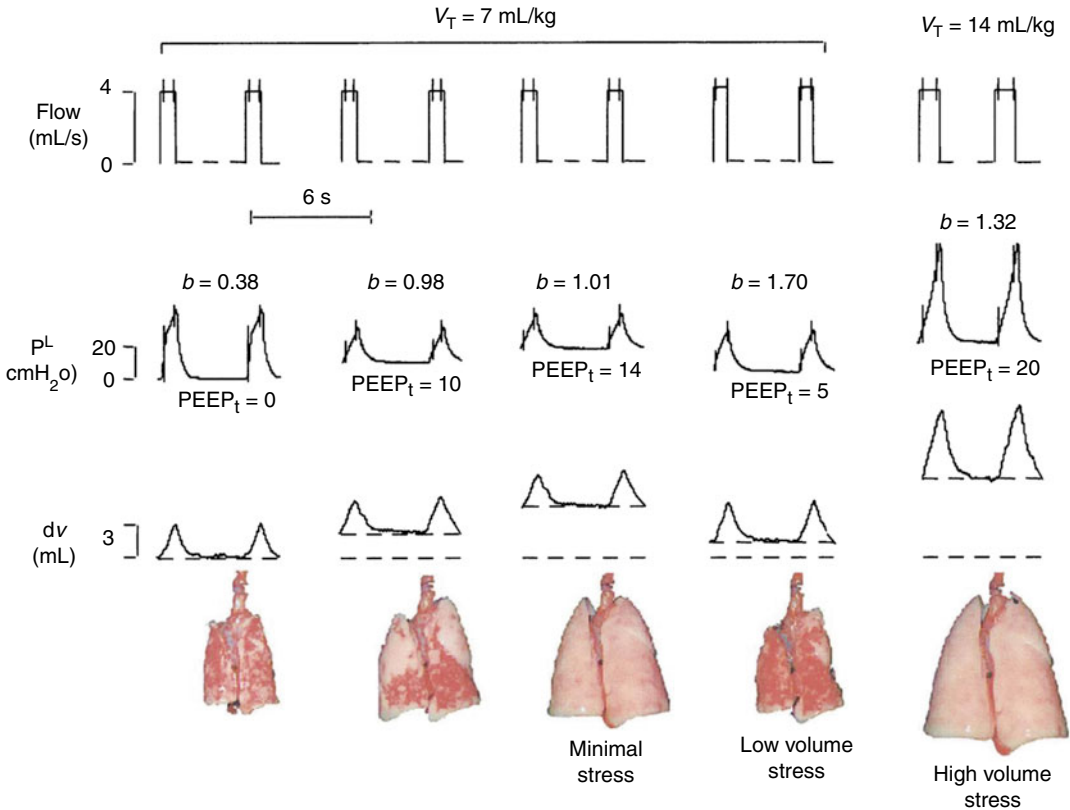


Fig. 13.11 Representative data record showing physiologic variables (flow, transpulmonary pressure (PL) and changes in lung volume (ΔV)) and the appearance at end-expiration of the excised lung during the different experimental conditions. The equation $P_L = a \cdot t^b + c$ was applied to the inspiratory PL during constant flow (vertical bars

on flow and PL). Low-volume stress, coefficient $b=0.5$, indicates ongoing recruitment; minimal stress, $b=1$, indicates no ongoing recruitment or overdistention; and high-volume stress, $b=1.5$, indicates overdistention. PEEP positive end-expiratory pressure (Reprinted with permission from Ranieri et al. (2000))

fact that there are no points of a zero flow condition attained at any point of the oscillatory cycle (Fig. 13.12). Similarly, the *Least-Squares Regression Method* applies the general equation of motion to a single compartment model (Stocks et al. 1996). Again, analysis has to be between two points of the pressure–volume curve, in this case taken from slope of the line joining the maximal and minimal volume. Again, the complex nature of pressure and flow waves, and attenuation, limits this methodology during HFV.

In contrast, the multiple linear regression technique uses the entire respiratory cycle to calculate Crs (Stocks et al. 1996). This method is valid during the complex pressure and flow conditions of HFV but requires an analytic process that involves applying an algorithm to minimise errors between the observed pressure changes

and the assumed pressure behaviour using the equation of motion for the flow and volume measurements. Multiple linear regression is currently impractical outside of a research environment.

13.1.2.2.5 Alternatives to Crs During HFV to Describe Respiratory Mechanics

In a state where the resistance of the ETT and ventilator circuit, lung disease, flow and applied ΔP are constant, it stands to reason that any change in measured HFV V_T (V_{THFV}) at the airway opening would be due to a change in Crs (Rossing et al. 1981; Slutsky et al. 1981; Wright et al. 1981). V_{THFV} can be measured at the airway opening using pneumotachography (Boynton et al. 1989; Dimitriou et al. 1998; Kamitsuka et al. 1990; Scalfaro et al. 2001; Watson and Jackson

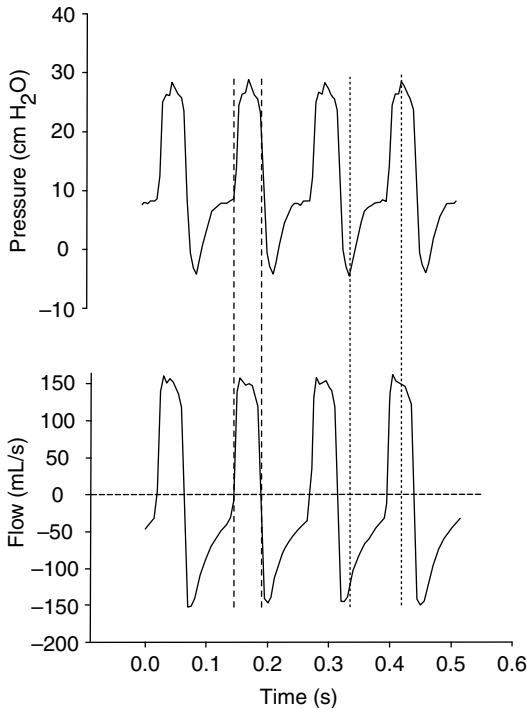


Fig. 13.12 Airway pressure (cm H₂O) and flow (mL/s) waveforms measured at the airway opening during four oscillatory cycles (Sensormedics 3100A high-frequency oscillatory ventilator) in a term infant with meconium aspiration syndrome. The Mead-Whittenberger method of determining dynamic C_{rs} cannot be applied as the two points of zero flow during each oscillatory cycle (*dashed lines*) do not correlate with the peak and trough of the pressure wave form (*dashed lines*)

1984; Zimova-Herknerova and Plavka 2006) and correlated well to plethysmographic measurement of tidal volume (Courtney et al. 1990). This method has been shown to be feasible and accurate in adults receiving HFOV for ARDS (Hager et al. 2007; Hager et al. 2006). A relationship between P_{aw} , volume state of the lung, lung volume and stroke volume (i.e. tidal volume during high frequency ventilation; V_{THFV}) V_{THFV} has been identified in 15 preterm infants with acute RDS receiving HFOV during the application of an open lung ventilation strategy to map the pressure–volume relationship of the lung (Miedema et al. 2012). Electrical impedance tomography measures regional end-expiratory thoracic volume and tidal volumes during HFOV, quantifying that V_{THFV} changes at the airway opening were indicative of regional lung recruitment, overdistension and collapse. This suggests

that V_{THFV} is at least functionally representative of CRS. Measurement of tidal volume at the airway opening may be a useful relative indicator of the alveolar tidal volume during HFOV.

During HFV the carbon dioxide diffusion coefficient (DCO_2) can be used to mathematically describe alveolar ventilation and CO_2 elimination (Rossing et al. 1981; Slutsky et al. 1981; Chang 1984). DCO_2 is proportional to the product of the frequency and the square of tidal volume (Chang 1984). Using this formula, an increase in either frequency or tidal volume should improve CO_2 elimination. This is in contradiction to the clinical observation that a reduction in frequency improves CO_2 elimination and illustrates the importance of using HFV at a frequency appropriate for the disease state and resultant lung mechanics. In addition, many high-frequency ventilators are unable to maintain a constant stroke volume over their operating range of frequencies (Hatcher et al. 1998). Some modern mechanical ventilators monitoring systems display DCO_2 .¹ This is calculated from the measured frequency at the airway opening and the square of V_{THFV} , as such it should be considered a proxy of alveolar ventilation. In situations in which the applied frequency and R_{rs} are constant, DCO_2 will only be influenced by C_{rs} (V_{THFV}).

There is little published data on the use of V_{THFV} or DCO_2 measured at the airway opening to monitor changes in C_{rs} during HFV. Mean airway pressures resulting in overdistension and atelectasis caused a reduction in V_{THFV} in healthy and surfactant-deficient piglets (Mills 2003, PhD Thesis, University of Melbourne). V_{THFV} improved after alveolar recruitment. A similar relationship between V_{THFV} (and DCO_2), applied pressure and resultant volume state of the lung was demonstrated in a small study involving 15 term and near-term infants receiving HFV using a lung volume optimisation strategy (Tingay et al. 2013). In this study, frequency and ΔP were held constant throughout a series of P_{aw} changes aimed to, firstly, recruit the lung to near total lung capacity and then identify the closing pressure of the lung and apply ventilation on the deflation limb of the pressure–volume relationship

¹ Some commercially available ventilators use the term high-frequency minute ventilation (MV_{HFV}). This is interchangeable with DCO_2 .

(Tingay et al. 2006). These findings support the observation of Miedema and co-workers (Miedema et al. 2012) that the resultant V_{THFV} and DCO_2 relationships with lung volume and P_{aw} were due to changes in Crs (Fig. 13.13). A definitive relationship between volume state of the lung and V_{THFV} or DCO_2 could not be demonstrated in every infant, illustrating the limitations of being solely dependent on one independent proxy value of Crs during HFV. It is possible that significant changes in the volume state of the lung may be required to noticeably alter V_{THFV} . Chan et al. (1993) found no change in tidal volume during increases in P_{aw} up to 5 cm H_2O above that required during IPPV.

Intermittent sampling of the arterial partial pressure of CO_2 (PaCO_2) is frequently used by clinicians to determine the correct amplitude and frequency during HFV. The relationship between PaCO_2 and P_{aw} during HFV is poorly understood. In some cases, no relationship between P_{aw} and PaCO_2 could be identified (Slutsky et al. 1981; Wright et al. 1981). In contrast, the presence of hypercarbia is more likely using a P_{aw} that results in overdistension, in both animal models (Mills 2003; Walsh and Carlo 1988; Yamada et al. 1986) and preterm infants (Chan and Greenough 1994). Breen et al. (1984) reported an improvement in arterial partial pressure of PaCO_2 at higher P_{aw} in the saline-lavaged lung, presumably due to inadequate recruitment at lower P_{aw} .

Transcutaneous measurement of CO_2 (TcCO_2) is a commonly used, and reliable, method of monitoring PaCO_2 trends, and hence CO_2 elimination, during mechanical ventilation in infants (Tingay et al. 2006, 2013). TcCO_2 monitoring has been advocated as mandatory during HFV (Froese and Kinsella 2005; van Kaam 2013). In a study of 103 preterm infants receiving HFV for hyaline membrane disease, TcCO_2 was found to be 1.2 kPa lower, despite the amplitude and frequency being held constant, after a lung volume optimisation manoeuvre designed to recruit the lung and apply ventilation on the deflation limb of the pressure–volume relationship (De Jaegere et al. 2006). The authors concluded that this difference was due to the improved lung mechanics. The relationship between TcCO_2 and the volume state of the lung was also systematically examined in the smaller

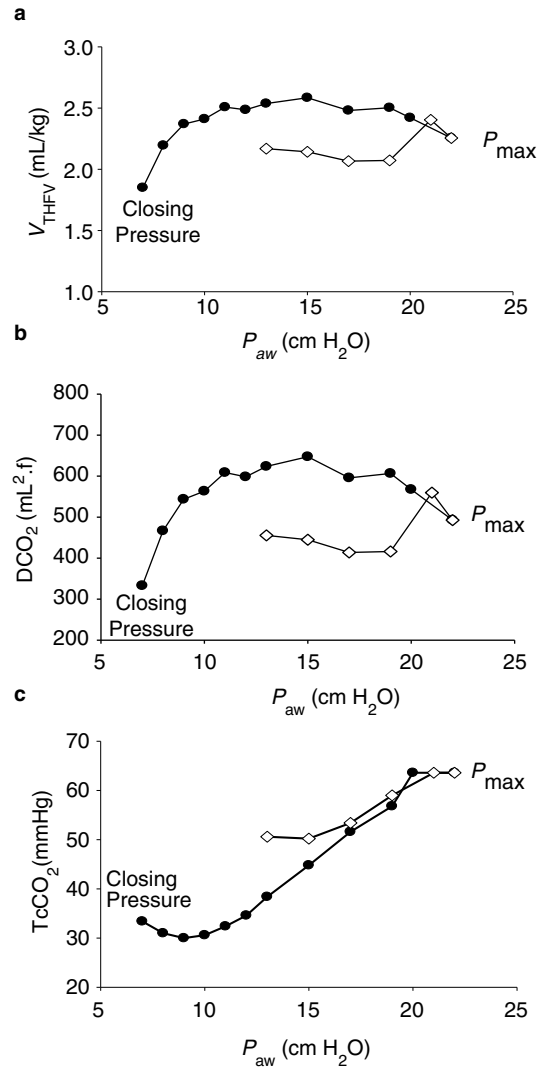


Fig. 13.13 Representative data from a term infant receiving HFV for meconium aspiration syndrome demonstrating the potential of V_{THFV} (a), DCO_2 (b) and TcCO_2 (c) to identify changes in the volume state of the lung during a series of P_{aw} changes designed to recruit the lung (open diamonds) to near total lung capacity (P_{max}), and then map the deflation limb of the pressure–volume relationship (closed circles) to the closing pressure of the lung. Amplitude and frequency were held constant at all P_{aw} , suggesting that resultant changes in all parameters are due to changes in Crs. All parameters were able to demonstrate improvement after recruitment, possible overdistension near P_{max} and worsening atelectasis once the closing pressure was obtained

studies of Miedema and co-workers (Miedema et al. 2012) (preterm infants) and Tingay and co-workers (Tingay et al. 2013) (term infants). In the recruited lung during HFV, the P_{aw} that

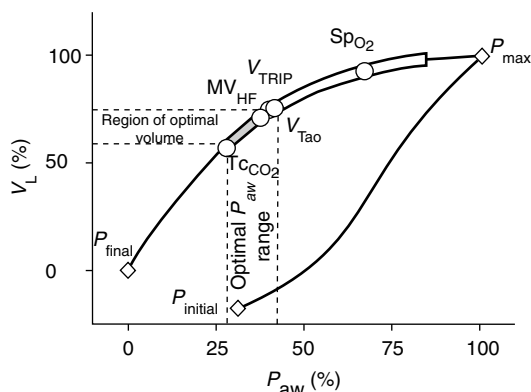


Fig. 13.14 Normalised pressure–volume relationship (black line) from 15 infants during an open lung strategy using HFV, fitted to the sigmoidal relationship described by Venegas et al. The region of the deflation limb encompassing <2 % difference from the maximal Sp_{O_2} value (crossed circle) obtained from lung recruitment to maximal P_{aw} is shown with a wide white band. Within this part of the deflation limb, there exists a narrow range of P_{aw} and resultant end-expiratory thoracic volume measured by respiratory inductive plethysmography (V_L) (grey filled band) in which transcutaneous partial pressure of carbon dioxide ($TcCO_2$), tidal volume at the airway opening (V_{Tao}), tidal volume measured by respiratory inductive plethysmography (V_{TRIP}) and high-frequency minute volume at the airway opening (MV_{HF}) (circles) were optimised while still maintaining the oxygenation benefit after recruitment to P_{max} . Pressure values for each optimal point are derived from the actual mean P_{aw} data; volume values are derived from the Venegas sigmoidal equation. P_{final} =final P_{aw} obtained (closing pressure) during pressure–volume mapping protocol; $P_{initial}$ = P_{aw} in use prior to open lung manoeuvre; Sp_{O_2} =oxygen saturation (Reprinted with permission from Tingay et al. (2013). © 2013 by the Society of Critical Care Medicine and Lippincott Williams and Wilkins)

optimised $TcCO_2$, DCO_2 and V_{THFV} has been shown to be closely related to each other and correlates with the lowest P_{aw} that maintain oxygenation and prevent derecruitment (Tingay et al. 2013) (Fig. 13.14). This point of ventilation, which is approximately 2–4 cm H_2O above the closing pressure of the lung, is often cited as the optimal P_{aw} to apply HFV (De Jaegere et al. 2006; Rimensberger et al. 2000b). Similar to V_{THFV} , $TcCO_2$ could be used to determine overdistension, collapse and the P_{aw} that optimised ventilation in most, but not all subjects (Tingay et al. 2013). Clearly, the limitations of $TcCO_2$ need to be considered. These findings do support the recommendation that when ‘ CO_2 elimination is a

Essentials to Remember

- For assessment of disease evolution, dynamic compliance measurements are of limited value, whereas measurements of static respiratory system compliance will give more information.
- Dynamic compliance measurements during ongoing mechanical ventilation are of limited value; analysis of the shape of the pressure–volume loop is often more helpful for choosing the best ventilator settings.
- Monitoring dynamic compliance can be helpful for incremental and decremental PEEP titration to find ‘best PEEP’ settings.
- Additional monitoring to compliance measures like CO_2 -elimination (DCO_2) as a marker of the efficiency of alveolar minute ventilation can be very helpful.
- Static compliance (Cr_s) can be used to determine the optimal application of high-frequency ventilation (HFV); however monitoring of static Cr_s in patients receiving HFV is difficult as it requires cessation removal from tidal ventilation.
- Monitoring of dynamic Cr_s is problematic during HFV; however, monitoring of HFV V_T (V_{THFV}) at the airway opening could be used, since any change in V_{THFV} would be due to a change in Cr_s.
- During HFV the carbon dioxide diffusion coefficient (DCO_2) can be used to mathematically describe alveolar ventilation and CO_2 elimination. DCO_2 is proportional to the product of the frequency and the square of tidal volume ($F \times V_{THFV}^2$).
- Additional monitoring to indirect compliance measures by V_{THFV} and/or $F \times V_{THFV}^2$ (often labelled as ‘ DCO_2 ’ on many HFV-ventilators) is needed during HFV. For this transcutaneous measurement of CO_2 ($TcCO_2$) during HFV is a commonly used, and reliable method of monitoring $PaCO_2$ trends, and hence CO_2 elimination, during mechanical ventilation in infants.

problem the first action must be to ensure adequate recruitment' (Froese and Kinsella 2005).

13.2 Respiratory System Resistance

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Sven M. Schulzke

Educational Aims

This chapter summarises the methods for the measurement of respiratory resistance in the clinical setting including pitfalls and clinical implications.

13.2.1 Resistance in Intubated and Non-intubated Patients

Resistance can be regarded as the pressure needed to generate a certain gas flow. It is calculated by the pressure difference divided by the air flow. Respiratory system resistance (R_{rs}) includes the resistances of the airway, lung tissue and the chest wall, and in the intubated child, it will additionally include the resistance of the endotracheal tube (ETT). In the non-intubated patient, the upper airway has a major impact on the respiratory system resistance, particularly in neonates and infants with small upper airway diameter, low upper airway muscle tone and structural instability of cartilaginous tissue. In pre-school children narrowing of the upper airway (e.g. caused by adenotonsillar hypertrophy) is commonly found. However, in an intubated child, the upper airway is bypassed with the ETT thus reducing the upper airway resistance but at the same time adding the resistance of the ETT.

13.2.2 Confounding Factors for the Measurement of Respiratory Resistance

In order to compare serial measurements, it has to be ensured that all measurements are taken at the same baseline setting with regard to ventilator

settings, size and length of the ETT, sedation and other agents administered. For example, sedation and even more so anaesthesia, particularly when muscle relaxants are used, will significantly impact on muscle tone and might also have bronchodilatory effects depending on the agent used (e.g. ketamine, inhalational anaesthetics) altering the resistance measured. Furthermore, the use of an uncuffed ETT is associated with leakage around the ETT which can jeopardise the correct measurement of respiratory mechanics.

13.2.3 Measurement Methods During Ongoing Mechanical Ventilation

Measurements of respiratory mechanics (R_{rs} and C_{rs}) can be divided into dynamic and passive (static) measurements. While dynamic measurements are taken during the respiratory cycle, the passive measurements are obtained during a brief interruption in the respiratory cycle, during which the respiratory muscles need to be relaxed to allow pressure equilibration. Although both measurements correlate well with each other, the values obtained by the passive technique are higher than those with the dynamic technique (Kugelman et al. 1995).

13.2.3.1 Passive Measurement of Respiratory Resistance

13.2.3.1.1 Single-Breath Occlusion Technique

Passive measurements of R_{rs} are based on a number of assumptions (Table 13.1). However, these assumptions have even been questioned not only in the child with lung disease but also in healthy children (American Thoracic Society/European Respiratory Society 1993; Fletcher et al. 1991). Additionally, only larger changes in R_{rs} can be detected since the intra-measurement coefficient of variation is approximately 10 % (Katier et al. 2005).

13.2.3.2 Measurement Technique

In the intubated child under assisted ventilation, the analysis of airflow, volume and pressure is

Table 13.1 Assumptions for the passive measurements of respiratory resistance and examples for deviations from assumptions

Assumption for the passive measurements of respiratory resistance (R_{rs})	Examples for deviation from assumptions
Single compartment respiratory system	Lung disease with air trapping
Inertance minimal	Very high ventilator rates
Respiratory muscles completely relaxed during occlusion and exhalation	Artefacts, differences in the sedated or anaesthetised child
Complete pressure equilibration during occlusion	Severe airflow limitation (e.g. asthma)
Stable respiratory mechanics throughout the breathing cycle	Decreased R_{rs} during inspiration, Increased R_{rs} during expiration

performed at a time of the breathing cycle when the respiratory muscles are inactive. This is usually achieved by a brief occlusion manoeuvre leading to a short respiratory pause. This causes the activation of stretch receptors in the chest wall leading to a short phase of apnoea and respiratory muscle relaxation. The occlusion manoeuvre stops the airflow thus allowing the pressures to equilibrate. Following complete equilibration, the airway opening pressure reflects the pressure within the alveoli and thus the elastic recoil of the respiratory system.

In the intubated child under controlled mechanical ventilation, passive respiratory mechanics can be determined using a single-breath occlusion, passive-deflation technique (Le Souef et al. 1984, 1986). Measurement of R_{rs} is performed by interrupting airflow close to end-inspiration during mechanical ventilation. It is crucial that the shutter is occluded long enough to obtain a sufficiently long-pressure plateau to allow for equilibration with alveolar pressure.

In both techniques (assisted and controlled ventilation), the resulting passive exhalation is then analysed for flow, relaxation airway pressure and volume to calculate C_{rs} and R_{rs} by drawing a regression line to the linear portion of the curve at a lung volume above FRC. R_{rs} can then

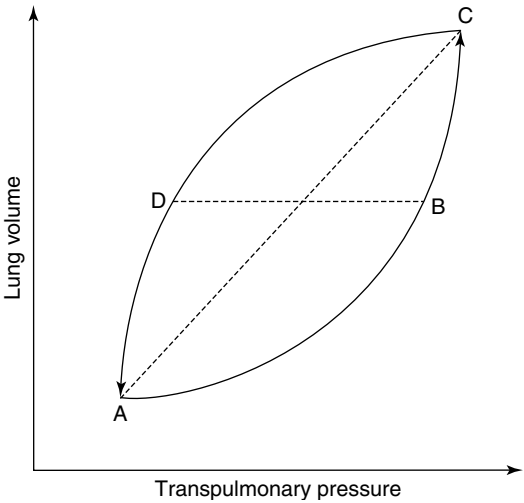


Fig. 13.15 Mead and Whittenberger graphical method of calculating resistance and compliance of the respiratory system. Lung volume is plotted against transpulmonary pressure. Dynamic compliance is derived as the slope of line AC. Dynamic resistance is calculated as the pressure drop due to resistance at midtidal volume between points B and D divided by the absolute sum of the inspiratory and expiratory flows at points B and D

be calculated either via the time constant ($T_{rs} = R_{rs} \times C_{rs}$) or by back extrapolating the slope of the linear decay to the point of the release of the occlusion ($R_{rs} = \text{change in pressure at airway opening/change in flow}$). Three to five acceptable manoeuvres are required for a valid analysis (Gappa et al. 2001).

13.2.3.3 Active Measurements of Respiratory Resistance

13.2.3.3.1 Mead-Whittenberger Method

The respiratory system can be modelled using a three-element consolidated model consisting of an elastic chamber, a tube acting as a resistance to gas flow and inertia of the mass of the chamber and gas (Heldt 1994). The equation of motion for such a system is as follows:

$$P = (1/C)V + RV + IV \quad (13.1)$$

where P is the pressure that inflates the volume V in the chamber through the inverse of the compliance C . Resistance R relates P to flow

while inertia I relates pressure to volume acceleration. The approach of *Mead and Whittenberger* (Mead and Whittenberger 1953) offers a graphical solution to the equation of motion (Fig. 13.15).

The authors assumed that (a) changes in transpulmonary pressure at zero flow (i.e. at end-inspiration and at end-expiration) are due only to elastic recoil, that (b) the change in transpulmonary pressure between inspiration and expiration at midtidal volume are due only to viscous forces and that (c) contribution of inertia to the total change in transpulmonary pressure is not relevant. Accepting these assumptions, terms one and two on the right side of Eq. 13.1 are equal to zero and term three was ignored in their analysis. Newer types of ventilators offer measurements of dynamic resistance (R_e) and compliance (C_{dyn}), mostly based on the Mead and Whittenberger method. Although such an approach provides non-invasive measurements of R_e that can be clinically useful for monitoring of changes in R_e over time, one needs to be aware that R_e is assumed to be constant within each breath (i.e. dynamic changes of R_e within the respiratory cycle cannot be detected) and that its estimates are based on only two points within the respiratory cycle.

13.2.3.3.2 Multiple Linear Regression Method

Multiple linear regression (MLR) analysis of pressure, flow and volume signals allows for computerised evaluation of R_e . Data are sampled continuously throughout each breath; thus, the equation of motion can be solved using a least squares fit (Lanteri et al. 1995; Nicolai et al. 1991). The advantage of this method is its independency of any particular flow waveform pattern and the potential to calculate R_e for inspiration and expiration separately; however, R_e values will vary with lung volume (Rousselot et al. 1992). Additionally, the MLR method is susceptible to errors caused by offsets in baseline flow and requires zero flow correction (Peslin et al. 1994). For a more detailed discussion of the MLR method, refer to Chap. 11.5.6 and 11.8.2.

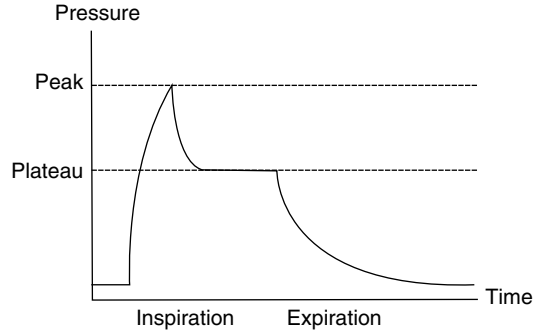


Fig. 13.16 Pressure–time curve during volume-controlled ventilation allowing the approximation of respiratory resistance by dividing the pressure difference (peak airway pressure–plateau pressure) by the airflow

13.2.3.3.2.1 Dynamic Bedside Assessment

During volume-controlled ventilation, R_e can be approximated by deducting the plateau pressure from the peak inspiratory pressure during a respiratory pause in the ventilator settings or a ventilator hold manoeuvre (Fig. 13.16):

$$\Delta P \left(\begin{array}{l} \text{peak inspiratory pressure} \\ - \text{plateau pressure} \end{array} \right) = R_e \times V'$$

13.2.4 Clinically Important Implications

13.2.4.1 Measurement of Resistance to Guide Ventilation Strategies

To our knowledge, the measurement of resistance has not been shown to improve outcome of patients. However, since R_e values are readily available on most modern intensive care ventilators, passive measurements of R_{rs} are rarely used in routine clinical practice.

In case of high R_{rs} due to air flow limitation of lower airways (e.g. asthma), increasing the respiratory rate is associated with a shortening of the expiratory time and might therefore cause additional air trapping and thus intrinsic PEEP. Consecutively, this can lead to dynamic hyperinflation with deleterious hemodynamic compromise and shock and/or volutrauma (refer also to Chap. 11.5.3 and 8.1.3.5.4.1).

The principal aim of ventilator settings is to allow for an adequate expiratory time thus allowing prolonged expiration. The optimal inspiratory time is the value at which target tidal volume is met. High-inspiratory peak flow leads to an increase in R_{rs} and therefore a reduction in tidal volume, while low-inspiratory peak flow either leads to decreased tidal volume or, if inspiratory and expiratory time are coupled, to a shortened expiratory time and consecutively to an increase in intrinsic PEEP (Marik et al. 2002). Tidal volumes should therefore be reduced to the lowest values that allow adequate CO_2 removal without an increase of the intrinsic PEEP (Oddo et al. 2006). Finally, airway pressures may have to be higher than normal since they will not represent alveolar pressure in the case of high R_{rs} .

To avoid volutrauma, volume-controlled ventilation modes are often applied using low tidal volumes. However, R_{rs} increases with a decrease in lung volume due to collapse of the bronchiole, while increases in lung volume are commonly associated with a decrease in R_{rs} due to the increase in size of the bronchi.

With regard to PEEP strategy, extrinsic PEEP adjusted on the ventilator needs to be higher than intrinsic PEEP to facilitate sufficient air flow. This allows for adequate expiration as well as reliable triggering of the ventilator, particularly in patients with severe airway obstruction and hyperinflation.

13.2.4.2 Monitoring of Progression of Disease and Response to Treatment

Clinically, an increase in R_e often correlates with soft tissue retractions, contraction of auxiliary respiratory muscles and active contraction of abdominal muscles during expiration. Mechanical ventilation in the presence of obstructive airway disease is always challenging. Monitoring of R_e during mechanical ventilation offers the possibility to detect changes in R_e indicating ETT obstruction or dislocation towards the carina and worsening of disease in terms of development of significant airflow obstruction, such as in infants with evolving BPD, meconium aspiration syn-

drome or bronchiolitis. A decrease in R_e as a response to bronchodilator treatment usually indicates a positive therapeutic effect. However, treatment response may be masked by decreased lung volume in patients with airway obstruction and established hyperinflation. In these patients, bronchodilator treatment may decrease FRC, potentially resulting in elevated R_e caused by the loss in lung volume. Longer-term changes in R_e due to progression of disease may guide the clinician in changes to ventilatory management, e.g. an increase in R_e in infants with evolving BPD may prompt caregivers to consider re-evaluate current ventilation strategy in order to ensure appropriate expiratory time, PEEP and lung volume.

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Educational Goals

This chapter aims to describe:

- The theoretical basis and technique of RIP
- The measurement of tidal volume and changes in end-expiratory lung volume during mechanical ventilation using RIP, including the limitations of these measurements
- The potential applications for RIP in neonatal and paediatric intensive care, including during high-frequency ventilation and newborn resuscitation

This chapter will not discuss the use of RIP within the field of sleep medicine.

14.1 Respiratory Inductive Plethysmography

David Tingay and Peter A. Dargaville

14.1.1 Introduction

Respiratory inductive plethysmography (RIP) is a non-invasive method of measuring change in lung volume which is well-established as a monitor of tidal ventilation and thus respiratory patterns in sleep medicine. As RIP is leak independent, can measure end-expiratory lung volume as well as tidal volume and is applicable to both the ventilated and spontaneously breathing patient, there has been recent interest in its use as a bedside tool in the intensive care unit.

14.1.2 Technique

14.1.2.1 Theoretical Considerations

RIP determines change in lung volume by measuring the changes in both chest and abdominal volume displacements during tidal ventilation. In 1967, Konno and Mead, using the principle that there is a relationship between linear motion and volume displacement, showed that the chest wall operates with 2° of freedom and has two moving parts, the rib cage and the abdomen (Konno and Mead 1967). Additionally, in terms of motion of their surfaces, there is functional separation between the abdomen and the rib cage during

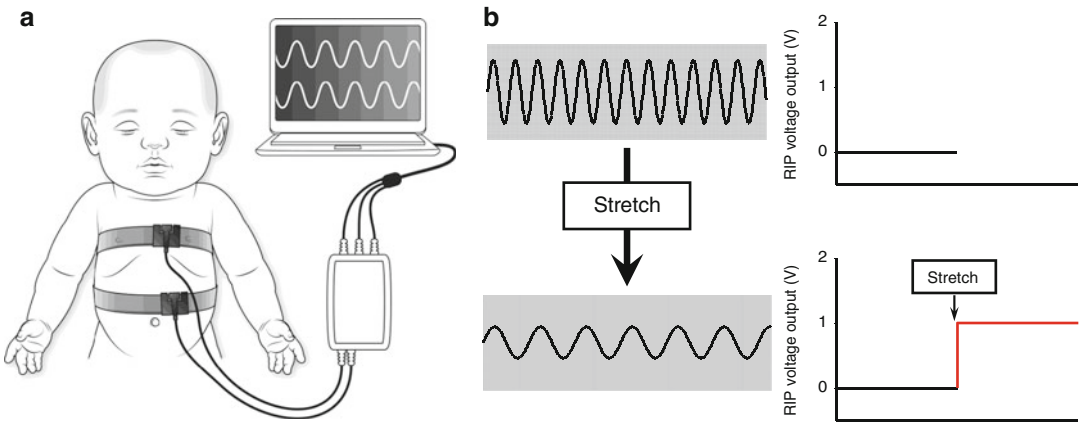


Fig. 14.1 (a) Illustration of RIP transducer bands correctly secured around the chest and abdomen of an infant. A sinusoidal wire embedded is in each band. (b)

Schematic illustration of the relationship between changes in RIP voltage output (V) generated by stretch of the sinusoidal wire secondary to change in lung volume

breathing. By utilising this unitary behaviour of the two compartments, change in total thoracic volume¹ can be determined from measurement of the volume displacement in each separate compartment. During ventilation, the lung will contribute to the majority of any thoracic volume change.

Thus, lung volume (V_L) can be mathematically expressed as follows:

$$V_L = V_{Lch} + V_{Lab} \quad (14.1)$$

where V_{Lch} and V_{Lab} represent volume displacement within the chest and abdominal compartments, respectively.

The true practical advantage of Konno and Mead's observation can be realised by considering the fact that a volume change will result in a change in cross-sectional area within each compartment.

Hence, V_L can be considered as

$$V_L = m(k \times \Delta R_{ch} + \Delta R_{ab}) \quad (14.2)$$

where R_{ch} and R_{ab} are the cross-sectional areas of the chest and abdomen compartments respectively, k is a proportionality constant, representing the relative contribution of each compartment to total volume, and m scales the sum of the

cross-sectional areas to a known volume (Sackner et al. 1989; Bar-Yishay et al. 2003).

14.1.2.1.1 Equipment

RIP systems employ two transducers, placed circumferentially around the chest and abdomen, to measure changes in the cross-sectional area of each (Watson et al. 1988; Adams 1996). Each transducer consists of a sinusoidal wire embedded in an elastic self-adherent material (Fig. 14.1). This allows the transducers to be applied to any chest or abdominal shape and size. One band is usually placed at nipple level (R_{ch}) and the other approximately 1 cm above the umbilicus (R_{ab}). These wires are connected to an electronic oscillator that generates a sine wave of 20 mV at 300 kHz. Stretch and relaxation of the bands produce variations in the electrical self-inductance within the wire and, thus, frequency (Adams 1996). The RIP unit demodulates the frequency change to produce an analogue voltage waveform representing the changes in rib cage and abdominal volume in real time (Ohms Law). The inductance within the wires increases linearly as a function of cross-sectional area in curved-shaped objects (Watson et al. 1988; Martinot-Lagarde et al. 1988; Brazelton et al. 1999a). The output of RIP is reliable within the frequency range of both conventional and high-frequency ventilator rates (Brazelton et al. 1999a, b; Boynton et al. 1989).

¹Total thoracic volume is the combined volume of gas, blood and tissue within the thoracic cavity.

Early RIP devices operated solely in AC-coupled output mode. This was adequate for assessing respiratory rate, tidal volume and synchrony of respiration, but the baseline signal was too unstable to assess end-expiratory lung volume (EELV) (Morel et al. 1983). Modern RIP devices allow both an AC- and DC-coupled output. In DC-coupled output, the RIP signal is sufficiently stable to allow reliable measurement of changes in EELV (Morel et al. 1983; Valta et al. 1992a), with good agreement with EELV values obtained by whole-body plethysmography (Carry et al. 1997) and super-syringe (Albaiceta et al. 2003).

14.1.2.1.2 Calibration

Changes in lung volume recorded by RIP are initially output as voltage changes. The RIP voltage change can be calibrated using a number of methods (Bar-Yishay et al. 2003). The two most common are the qualitative diagnostic calibration (QDC) algorithm (Sackner et al. 1989) and the least mean squares technique (Konno and Mead 1967; Strömberg et al. 1993). The least mean squares technique requires knowledge of a known volume change during the calibration phase, which is not always possible during paediatric and neonatal ventilation. For this reason, the QDC algorithm is the method most commonly used in ICU environments.

The QDC measures the voltage changes during a series of breaths at the start of the RIP recording, generally over 5 min. QDC allows derivation of the proportionality constant, k , in Eq. 14.2. The relative contribution of each compartment to the overall voltage change is estimated by selecting a series of breaths of similar tidal volume. This is achieved by excluding all breaths greater than one standard deviation (SD) of the mean ΔR_{ch} and ΔR_{ab} value. The constant k is then estimated as $SD(R_{ch})/SD(R_{ab})$ (Sackner et al. 1989). QDC has been shown to generate acceptable agreement with pneumotachograph measurement of tidal volume in term newborn infants (Adams 1996) and piglet models of surfactant-deficient lung disease (Markhorst et al. 2006). The reliability of RIP calibration is best when measurements are immediately pre-

ceded by calibration and tend to deteriorate with time. RIP calibration accuracy decreases with severity of lung disease. In vitro, the phase deviation in the transducer outputs, and thus the stability of the proportionality factor, increases in a linear fashion at frequencies above 10 Hz (Boynton et al. 1989). The accuracy of this process is also directly related to the number of breaths analysed (Brown et al. 1998).

If the volumetric changes during the QDC are known, for example, using a pneumotachograph or super-syringe, then the scaling factor, m , can be determined for Eq. 14.2, and the RIP signals displayed in units of volume (Fig. 14.2). Calibration and signal stability can then be maintained if the band location and tension remain constant and the patient's position, or pattern of breathing, does not change (Landon 2002).

An advantage of the QDC method is that it can still be applied when absolute volume changes are not known. In these circumstances, changes in relative volume can be expressed as a ratio to the tidal volume during the QDC period. This is useful during non-invasive ventilation (Courtney et al. 2001) and high-frequency ventilation (Markhorst et al. 2006; Habib et al. 2002; Weber et al. 2000; Markhorst and van Genderingen 2004; Copnell et al. 2009; Hoellering et al. 2008; Tingay et al. 2006, 2007a). After QDC, a modern RIP device has been found to have a mean relative measurement bias of -2.0 (SD 9 %) during short periods of high-frequency ventilation (HFV) in a piglet model of paediatric lung disease (Markhorst et al. 2006; Markhorst and van Genderingen 2004). This error is less than common commercially available pneumotachographs (Scalfaro et al. 2001; Roske et al. 1998). This study also demonstrated that a k factor of 1.0 was reasonable for most paediatric lung disease states, overcoming some of the difficulties associated with QDC during high-rate, low tidal volume ventilation.

14.1.2.2 Clinical Applications

14.1.2.2.1 Assessment of EELV

The capacity of DC-coupled output RIP to achieve a stable baseline signal offers the potential to reliably measure change in EELV during mechanical ventilation, particularly high-

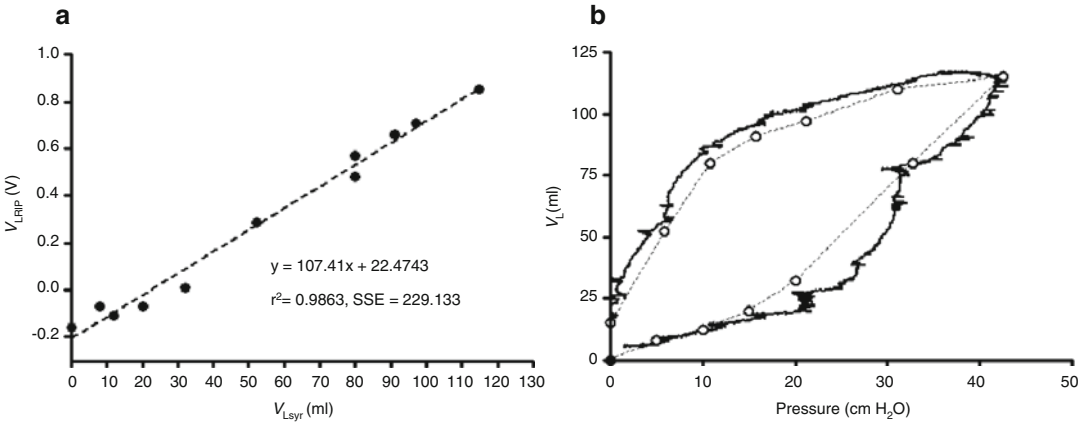


Fig. 14.2 (a) Relationship between super syringe volume (V_{Lsyr}) and RIP (V_{LRIP}) during a static pressure-volume curve between 0 and 40 cm H₂O in a preterm lamb. RIP demonstrates a strong correlation over a wide range of lung volumes. (b) Resultant pressure-volume relationship after calibrating the RIP unit (solid lines). Open circles; Pressure – V_{Lsyr} relationship

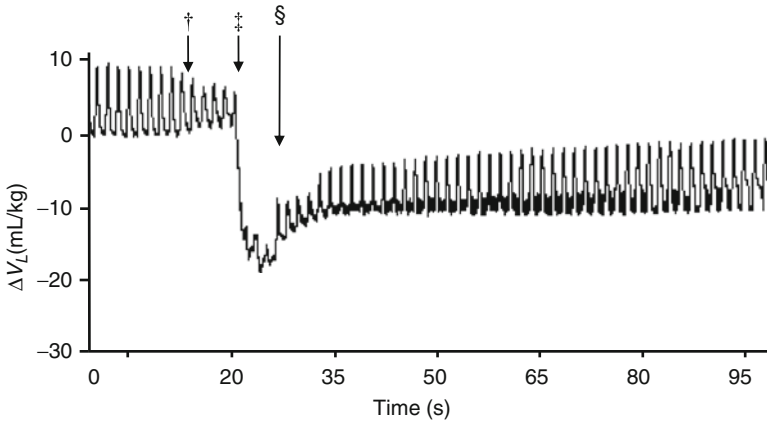


Fig. 14.3 Change in lung volume during endotracheal tube suction using a closed technique in an animal model of paediatric lung disease demonstrating the ability of RIP to document changes in both EELV and V_T . Insertion of the suction catheter into the endotracheal tube (†), ‡ application of negative pressure suction and § completion of suction process (Adapted from Copnell et al. (2009). Reproduced with permission © 2009 International Pediatric Research Foundation, Inc)

frequency and non-invasive ventilation. Most modern ventilators include continuous airway flow monitoring, allowing RIP to be calibrated easily and frequently during conventional forms of mechanical ventilation.

14.1.2.2.1.1 Conventional Mechanical Ventilation

The first use of RIP to measure EELV was in an adult population after open heart surgery (Valta et al. 1992a, b). In this study, RIP was successfully used to measure the $\Delta EELV$ at different

PEEP levels. This suggests that RIP may have potential to define an optimal PEEP during conventional mechanical ventilation in the paediatric population. RIP has frequently been used to measure $\Delta EELV$ during endotracheal tube suction (Copnell et al. 2009; Hoellering et al. 2008; Choong et al. 2003) (Fig. 14.3). In these studies, RIP has been able to accurately identify small changes in absolute and relative $\Delta EELV$ in infants and children ventilated with (Choong et al. 2003) and without (Hoellering et al. 2008) muscle relaxants.

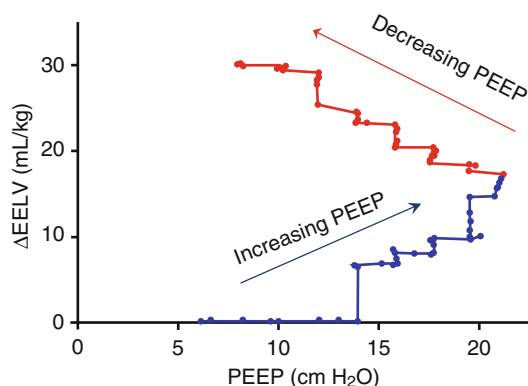


Fig. 14.4 Change in end-expiratory lung volume (mL/kg) during step-wise changes in PEEP in a preterm lamb. Ventilation applied using positive-pressure ventilation with a targeted tidal volume of 7 mL/kg

To date, there are no reports of the use of RIP as a guide to the optimal application of PEEP in the paediatric population, despite the potential RIP offers in this field. Pilot data in preterm lambs suggest that RIP can map Δ EELV very effectively during conventional mechanical ventilation (Fig. 14.4).

14.1.2.2.1.2 High-Frequency Ventilation

RIP has found a place in measurement of lung volume during high-frequency ventilation (HFV), in large part due to the difficulties in assessing volumetric change with other devices. The non-laminar gas flow during HFV makes pneumotachographic measurement of tidal volume difficult and measurement of EELV impossible (Gerstmann et al. 1990). RIP measures volume change directly within the thoracic cavity and is unaffected by flow characteristics. RIP thus has the potential to measure both tidal volume and EELV during HFV.

Calibrated RIP has been used to measure changes in lung volume during endotracheal tube suction in a small population of infants receiving HFV (Tingay et al. 2007a). This was achieved by calibrating the RIP voltage change against tidal volume at the airway opening in a series of tidal inflations during conventional ventilation. This technique requires transient discontinuation of HFV and, possibly, disconnection from mechanical ventilation. It is reasonable to conclude that

this method of calibration would be accurate for short periods during HFV. Whether the calibration factors remain accurate over longer periods is questionable, especially in states of severe, or changing, lung disease (Tingay et al. 2007b).

Even when uncalibrated, RIP still has clinical potential to measure relative changes in lung volume during HFV and avoids the limitations of calibration (Markhorst et al. 2006). On the bench-top, uncalibrated RIP accurately measures relative change in EELV during HFV between frequencies of 7 and 15 Hz (Brazelton et al. 1999a), with a stable signal for up to 4 h in a thermally constant environment (Brazelton et al. 1999b). Signal stability beyond 3 h has not been confirmed in human studies (Tingay et al. 2006).

Uncalibrated RIP has been shown to be a reliable method of assessing relative change in EELV during HFV in animal models of neonatal lung disease, agreeing with changes in lung volume measured using whole-body plethysmography (Weber et al. 2000), super-syringe-derived pressure-volume relationships (Brazelton et al. 2001; Gothberg et al. 2001) and single-slice chest computed tomography (Authors' unpublished data).

The first reported use of RIP to record changes in EELV during HFV was by Saari et al. (1984) in which dynamic hyperinflation was demonstrated in seven adult patients receiving high-frequency ventilation. More recently, RIP has been used to describe the relationship between applied P_{aw} and thoracic volume during HFV in animal models of surfactant-deficient lung disease. Identification of lung overdistension during sequential increases in P_{aw} was possible in the healthy and surfactant-depleted piglet lung using RIP-derived static compliance (Weber et al. 2000). In both lung models, the relationship between applied P_{aw} and compliance fitted a second-order sigmoidal model of the pressure-volume relationship (Venegas et al. 1998), with the P_{aw} resulting in overdistension translating to the upper inflection point of the sigmoid curve, suggesting that RIP could be used to describe the inflation limb of the pressure-volume relationship (Weber et al. 2000). The same group has also shown that RIP-derived time constants of the lung can be used to identify the point of optimal

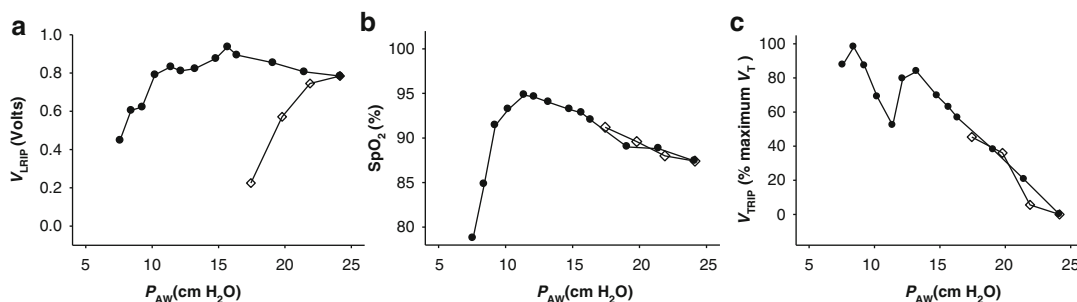


Fig. 14.5 (a) Relationship between mean airway pressure (P_{AW}) and EELV, measured with RIP (V_{LRIP}) during an open lung recruitment strategy in a muscle-relaxed term infant receiving HFOV for meconium aspiration syndrome. Open lung recruitment strategy consisted of a series of step-wise increases in P_{AW} (open diamonds) until

total lung capacity, followed by step-wise decreases (closed circles) until the closing pressure of the lung was identified by persistent desaturation (b). (c) Relationship between HFOV tidal volume, measured by RIP (V_{TRIP}) and normalised to the maximum V_{TRIP} identified, during the same open lung recruitment strategy

ventilation during sequential P_{aw} increases (Habib et al. 2002).

Increasingly, strategies which aim to apply HFV at the lowest possible P_{aw} that maintains lung volume after a recruitment manoeuvre are being advocated (Rimensberger et al. 1999a, b, 2000a, b; van Kaam and Rimensberger 2007; De Jaegere et al. 2006; van Kaam et al. 2003, 2004a, b; Lachmann 1992; Vazquez de Anda et al. 1999, 2000; Froese 1997). Mapping the volumetric response to recruitment is difficult at the bedside, and clinicians are limited to resorting to indirect indicators of lung volume, such as oxygenation. In a piglet model of paediatric acute respiratory distress syndrome (Brazelton et al. 2001) and term and preterm lambs (Gothberg et al. 2001), RIP has been used to demonstrate lung volume recruitment, hysteresis and subsequent optimal P_{aw} on the deflation limb of the pressure-volume relationship of the lung. In both these studies, critical points within the pressure-volume relationship, including total lung capacity, were identifiable. RIP can also demonstrate improvement in the hysteresis of the lung after administration of exogenous surfactant (Gothberg et al. 2001).

RIP has been used to map relative lung volume changes during an open lung recruitment strategy in 15 term to near-term muscle-relaxed infants receiving HFV (Tingay et al. 2006). RIP was used to determine the relationship between EELV and applied pressure, oxygenation and lung mechanics (Fig. 14.5). For the first time, lung recruitment,

hysteresis and the closing pressure of the lung could be identified during HFV in infants. In addition, a direct relationship between oxygenation and lung volume was confirmed. This study demonstrated that uncalibrated RIP could be reliably used over prolonged periods (up to 3 h) to track Δ EELV. Subsequently, the authors were able to demonstrate that RIP could determine the time when stable EELV had been achieved after a pressure change (Tingay et al. 2005).

14.1.2.2.1.3 Non-invasive Ventilation

Similar to HFV, application of non-invasive ventilation is to some extent hampered by a lack of reliable direct measures of lung volume. Despite the increasingly popularity of non-invasive modes of ventilation to treat neonatal and paediatric lung disease, a strategy to define optimal continuous distending pressure (CDP) remains elusive. Interestingly, the use of RIP to measure EELV during CPAP is limited to two studies in preterm infants (Courtney et al. 2001; Elgellab et al. 2001). In both studies, RIP was able to track the relationship between PEEP and EELV during a series of PEEP changes from 0 to 8 cm H₂O. One study measured relative Δ EELV using the RIP-determined V_T value as a unit of volume (Elgellab et al. 2001). The other calibrated the RIP signal to the pneumotachograph V_T during a brief period of spontaneous breathing through a face mask (Courtney et al. 2001), a technique that has been validated previously (Brooks et al. 1997). Both

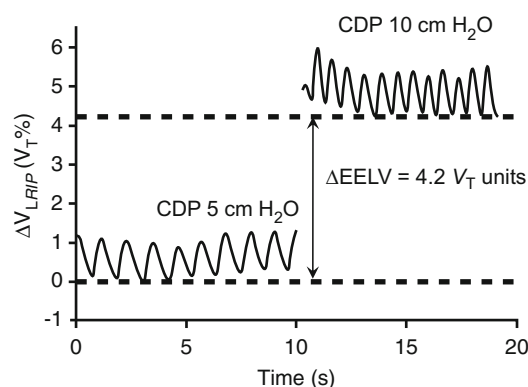


Fig. 14.6 Uncalibrated RIP tracing in a preterm infant receiving CPAP at a continuous distending pressure (CDP) of 5 cm H₂O and 10 cm H₂O. RIP is able to demonstrate tidal volume, respiratory rate and change in end-expiratory lung volume (Δ EELV). RIP units expressed as a proportion of the average tidal volume during the 5 cm H₂O tracing

calibration techniques would be clinically reproducible. The results of both these studies suggest that RIP may be useful in determining the optimal CDP during CPAP (Fig. 14.6).

14.1.2.2.2 Assessment of Tidal Volume and Breathing Patterns

The first use of RIP to assess tidal breathing patterns in spontaneously breathing infants was described by Duffty et al. (1981). Since then, RIP has been used extensively to assess tidal volume, thoraco-abdominal asynchrony and work of breathing in infants (Strömberg et al. 1993; Courtney et al. 2001; Habib et al. 2002; Dolfen et al. 1982; Tabachnik et al. 1981; Stefano et al. 1986; Adams and Zabaleta 1993a, b, 1994). These initial studies demonstrated the accuracy of RIP in measurement of V_T , in calibrated and uncalibrated modes, even over long periods of time (Brooks et al. 1997). The accuracy of RIP compared favourably with impedance sensors and strain gauges (Adams and Zabaleta 1993b). Apart from a direct measure of tidal volume, RIP allows the potential to assess the respiratory effort and pattern over time. As RIP is a measure of chest wall and abdominal movement, detection of apnoea is possible (Brooks et al. 1997; Weese-Mayer et al. 2000). During spontaneous breathing, knowledge of the synchrony of the

abdominal and thoracic compartments is important as the summated signal constitutes the measured tidal volume. If the two compartments are out of phase (paradoxical breathing), there is the potential for the summated time course signal to indicate no tidal ventilation (Fig. 14.7). Such states of significant asynchrony of thoraco-abdominal motion signify poor lung mechanics and lead to significant diaphragmatic work and fatigue (Musante et al. 2001; Schulze et al. 2001; Guslits et al. 1987).

14.1.2.2.2.1 Conventional Mechanical Ventilation

Due to the availability, relative ease and reliability of pneumotachographic assessment of tidal volume at the airway opening, there are very few reports of assessment of tidal volume using RIP during conventional mechanical ventilation. RIP has been used to identify improved tidal volume, thoraco-abdominal synchrony and chest wall displacement after transition to proportional assist ventilation from CPAP (Musante et al. 2001).

RIP has been shown to be a reliable alternative to pneumotachography in driving ventilator synchronisation during conventional mechanical ventilation in animal models of the normal and diseased paediatric lung (Schulze et al. 2001). The accuracy of the RIP bands was depended on a reliable calibration of the contribution of each band to the summated signal. This accuracy diminished significantly after body movement, limiting the use of the summated signal for prolonged mechanical ventilation periods in ICU. Schulze et al. have proposed that the use of the abdominal band alone would overcome these difficulties and offer the advantage of being a leak- and dead-space-free method of determining spontaneous respiratory effort (Schulze et al. 2001).

Pneumotachography will be unreliable during states of rapid compliance change or respiratory asynchrony, such as endotracheal tube suction (Copnell et al. 2009; Hoellering et al. 2008) and surfactant administration. During these situations, RIP is likely to be a better indicator of tidal volume change in the thorax.

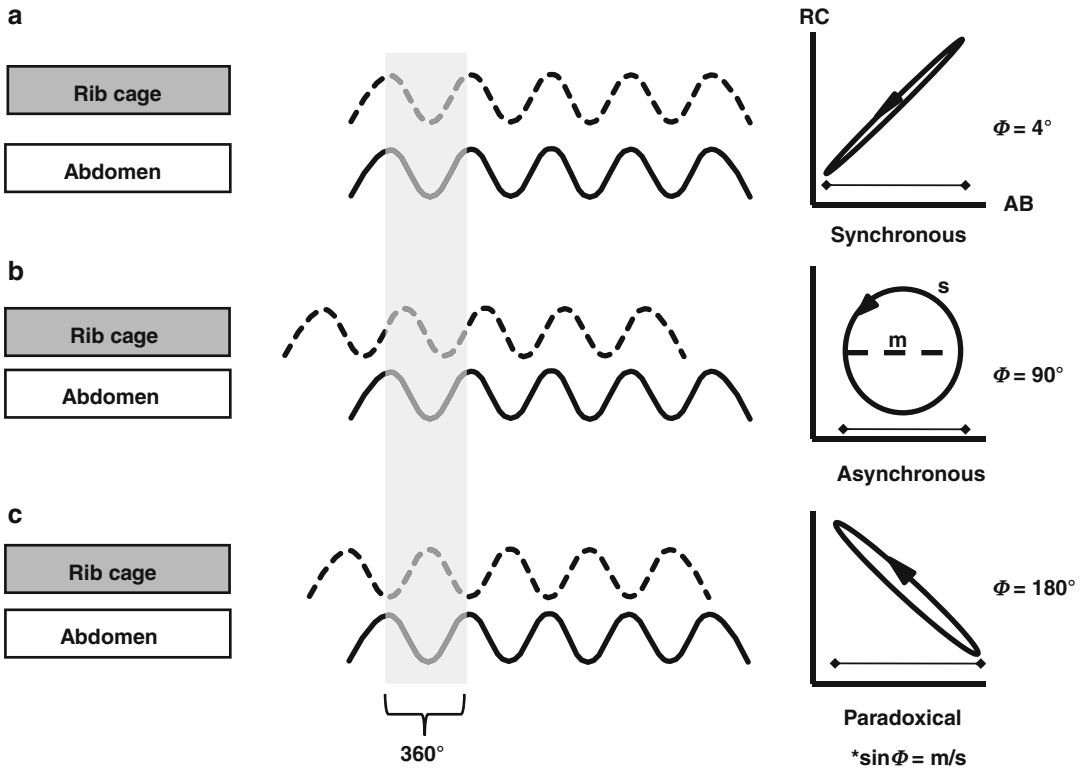


Fig. 14.7 RIP waveforms during tidal ventilation to illustrate synchronous (in phase; **a**), asynchronous (**b**) and paradoxical (completely out of phase; **c**) patterns of thoraco-abdominal motion. The resultant Lissajous plot (Konno-Mead plot) of rib cage (RC) against abdomen (AB) displacement during a single breath (highlighted in

grey) shown on the *right*. Phase angles of 0° indicate perfectly synchronous thoraco-abdominal motion and 180° completely asynchronous motion. Poor lung mechanics and respiratory muscle fatigue is associated with highly asynchronous states (Figure courtesy of Dr Christopher Newth)

14.1.2.2.2 High-Frequency Ventilation

Assessment of V_T during HFV is problematic. Pneumotachographic measures at the airway opening provide an accurate trend of HFV V_T in vitro (Scalfaro et al. 2001), but do not correspond with the volumetric changes measurable at the chest wall. The accuracy of pneumotachography during HFV in humans has not been confirmed (Zimova-Herknerova and Plavka 2006); thus, it should be considered at best a proxy for tidal changes more distally in the tracheobronchial tree. In contrast, RIP is a direct measure of chest wall movement during HFV and likely to be a better representative of tidal volume. In an animal model of paediatric acute lung injury, RIP tidal amplitudes could be accurately measured and altered accordingly with changing PEEP and compliance (Markhorst et al. 2005, 2006). RIP

tidal amplitude could then be used to identify overdistension during HFV. A similar relationship between volume state of the lung and RIP-derived V_T has been found in human infants receiving HFV (Fig. 14.5) (Tingay 2013). In this study, the RIP-derived V_T response approximated that of V_T measured by pneumotachograph (Tingay 2008).

14.1.2.2.3 Non-invasive Ventilation

The early descriptions of RIP in infants related to tidal patterns in spontaneously ventilated subjects (Strömberg et al. 1993; Duffty et al. 1981; Dolfin et al. 1982; Stefano et al. 1986). Compared to pneumotachography, RIP shows good agreement as a measure of V_T during CPAP and spontaneous ventilation in preterm infants (Bar-Yishay et al. 2003; Brown et al. 1998). Unlike face mask

pneumotachography, RIP offers the ability to monitor tidal ventilation without significant disruption and can determine the synchrony of ventilation using the phase angle between the chest and abdominal tidal signals, sometimes expressed as a laboured breathing index (LBI). RIP has been used to demonstrate the effect of alterations in continuous distending pressure on tidal breathing patterns in preterm infants receiving CPAP. A higher pressure (maximum 8 cm H₂O) resulted in a better V_T and thoraco-abdominal synchrony and lower LBI, suggesting less work of breathing (Elgellab et al. 2001). Courtney and co-workers also demonstrated an association between increased respiratory rate and greater phase angle with CPAP delivered via nasal cannulae compared with short binasal prongs (Courtney et al. 2001). These small studies suggest that RIP may be useful as a monitoring device during CPAP.

14.1.2.3 Limitations

The most important limitation of RIP is the inability to determine the residual volume of the lung and absolute volume change. Furthermore, change in inductance measured by RIP is linearly related to total thoracic volume rather than gas volume per se. We have noted that RIP detects blood volume change within the chest during intravenous administration of fluid boluses (Authors unpublished data).

Early RIP systems were also susceptible to significant thermal drift, limiting the capacity to accurately monitor Δ EELV (Bhatia et al. 2010). Some modern RIP devices require up to 60 mins to achieve signal stability in a stable ambient temperature (Tingay 2008; Bhatia et al. 2010), but thereafter, signal stability is excellent and, in many cases, better than pneumotachographs (Markhorst et al. 2006; Brazelton et al. 2001; Tingay 2008). Drift appears to be less of an issue in newer RIP systems (Bhatia et al. 2010). The disease state of the lung may also affect the drift of the RIP signal. RIP was found to be unreliable during mechanical ventilation in adults with severe obstructive pulmonary disease (Neumann et al. 1998; Werchowski et al. 1990).

Strict adherence to a standardised method of transducer placement is required to reduce

intersubject variability (Landon 2002). The chest and abdomen are most likely to operate with 1° of freedom when transducers are placed at the level of the nipples and at, or just above, the umbilicus (Konno and Mead 1967; Tingay et al. 2006; Brooks et al. 1997; Weese-Mayer et al. 2000). Most reports of RIP during paediatric critical care have equally weighted the chest and abdominal contributions. There is some evidence to support this assumption in paediatric acute lung injury (Markhorst et al. 2006), although it should be noted that this assumption is not universally true and may significantly alter measurement error (Poole et al. 2000).

The greatest hindrance for RIP is the lack of commercially available products specifically for intensive care use. Until RIP devices that measure changes in EELV and V_T are integrated into modern monitoring systems, the potential for RIP is limited to a research tool.

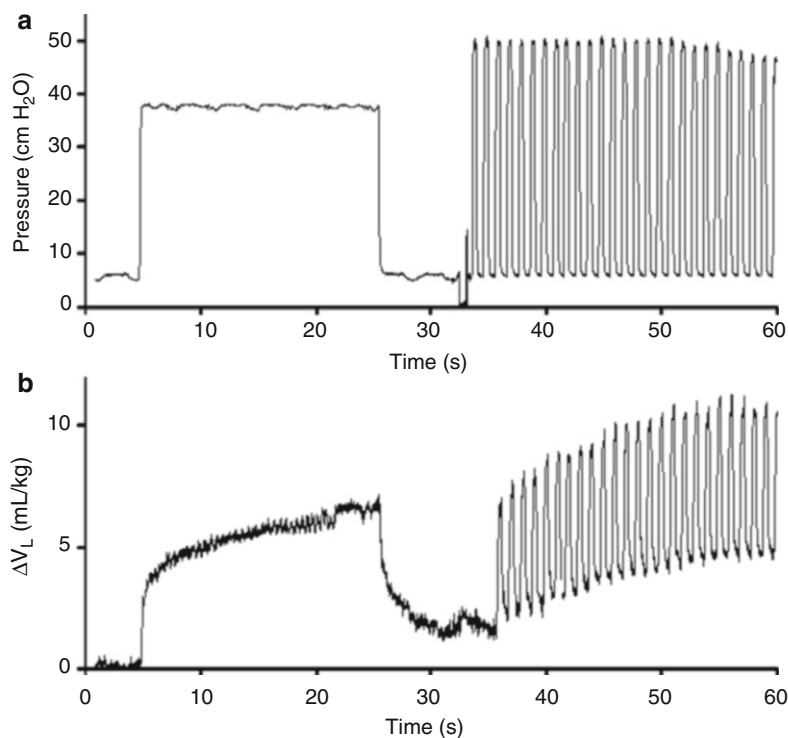
14.1.2.4 Future Directions

The use of RIP in the resuscitation of newborn infants has not been described. Birth is a time of significant volume change in the lung. Increasingly, the need to establish adequate aeration is being recognised. Theoretically, RIP may offer promise in this clinical environment. Preliminary data in animal models of prematurity show that RIP can demonstrate tidal and end-expiratory lung volume change during resuscitation at birth (Fig. 14.8). As bedside lung mechanics monitors incorporating airway flow, pressure and RIP measures become available, the potential for RIP to guide newborn resuscitation should be investigated.

Essentials to Remember

- RIP is a non-invasive method of measuring absolute or relative changes in thoracic volume.
- RIP is an accurate method of measuring breathing patterns and tidal volume, without the limitations associated with measurements at the airway opening.

Fig. 14.8 Change in airway pressure (**a**) and lung volume (calibrated RIP, mL/kg; **b**) during a sustained inflation applied at birth, followed by positive pressure ventilation, in a preterm lamb



- More recently, RIP has shown promise as a reliable method of determining $\Delta EELV$ in the mechanically ventilated patient.
- At present, RIP remains an important tool for respiratory research at the bedside in ICU.
- In the future, with development of commercially available RIP units that overcome some of the inherent limitations present in current systems, RIP has the potential to be a valuable monitoring tool in paediatric and neonatal intensive care.

Educational Aims

This chapter aims to give an understanding of:

- The plethora of information on the heterogeneity of lung disease, the response to recruitment and the distribution of aeration that has been gained by computed tomography
- The value of other imaging techniques, including magnetic resonance imaging and positron emission tomography, in the study of the diseased lung
- The limitations of these imaging techniques in ventilated infants and children

14.2 Lung Imaging Methods

Peter A. Dargaville

14.2.1 Computed Tomography

The purpose of this section is to detail the advances in understanding of the diseased lung and its response to ventilation that have been made with the assistance of computed tomography. The use of CT imaging as a diagnostic tool in the ventilated infant and child is not discussed.

14.2.1.1 What Have We Learned from Computed Tomography of the Lung?

Since the earliest reports of the appearances of the lung in a ventilated subject using axial CT imaging (Brismar et al. 1985), a considerable body of knowledge has accumulated regarding the abnormalities of inflation and aeration in the diseased lung. Valuable insights have been gained both from experimental studies in animal models of lung disease and from ventilated humans, most of whom have been adults with acute respiratory distress syndrome (ARDS) (Gattinoni et al. 2001). In view of the radiation hazard, CT imaging specifically for delineation of patterns of aeration has not been performed in any systematic way in ventilated neonates, infants or children, but much of the data obtained in adult humans has direct relevance to even the smallest ventilated subject. The key observations made using CT imaging of the diseased lung are sum-

marised in Table 14.1 and discussed further below.

A seminal observation from axial CT imaging in ARDS was that, in the face of relatively diffuse opacification on plain X-ray, lung densities are inhomogeneously distributed on axial CT slices (Fig. 14.9) (Gattinoni et al. 1986, 2001). It is now clear that ARDS is a patchy disease which includes areas of opacification and consolidation interspersed with regions in which relatively normal lung architecture and aeration remain. It is presumed that ARDS in infancy and childhood, as well as a number of neonatal lung diseases (including meconium aspiration syndrome), are similar morphologically. This has implications for the type of ventilation strategy to be used and its potential effectiveness, particularly if there are large areas of consolidation resistant to reinflation that are in juxtaposition with areas of relatively unaffected lung prone to hyperinflation.

Several descriptions of the morphological pattern of CT densities exist in ventilated patients with ARDS. The densities have been classed as diffuse, lobar or patchy (Puybasset et al. 2000), with the diffuse pattern being associated with a greater response to recruitment (Constantin et al. 2010). The pattern of lung densities has also been recognised to differ based on whether the lung disease is pulmonary or non-pulmonary in origin (Pelosi et al. 2003). In the latter case, the major impairment of compliance involves the chest wall, including the diaphragm, which may be subjected to significant limitation of movement in cases of abdominal sepsis or trauma (Pelosi et al. 2003). Not surprisingly, supra-diaphragmatic lung regions are most prone to atelectasis when there is diaphragmatic splinting of this type. Examples in childhood are a preterm infant with necrotising enterocolitis or a child with acute pancreatitis, but again no systematic CT imaging studies have been performed.

CT imaging in ARDS has also revealed that the inhomogeneous distribution of lung densities is, in part, gravity-related. The potential for superimposed pressure to cause compression atelectasis of dependent lung regions is now understood (Pelosi et al. 1994), as is the heightening of this effect in the diseased lung where the gas to tissue ratio is decreased throughout the

Table 14.1 Information derived from computed tomography of the diseased lung

Inhomogeneity of lung expansion even with a relatively diffuse disease on plain X-ray
Effect of superimposed pressure on the dependent regions of the diseased lung
Presence of aeration “compartments” – non-aerated, poorly aerated, normally aerated and hyperinflated – in the diseased lung
Changes in lung aeration and recruitment (reduction in non-aerated lung) during ventilatory manoeuvres
Estimation of the potential for recruitment
Coincidence of recruitment and hyperinflation during tidal ventilation

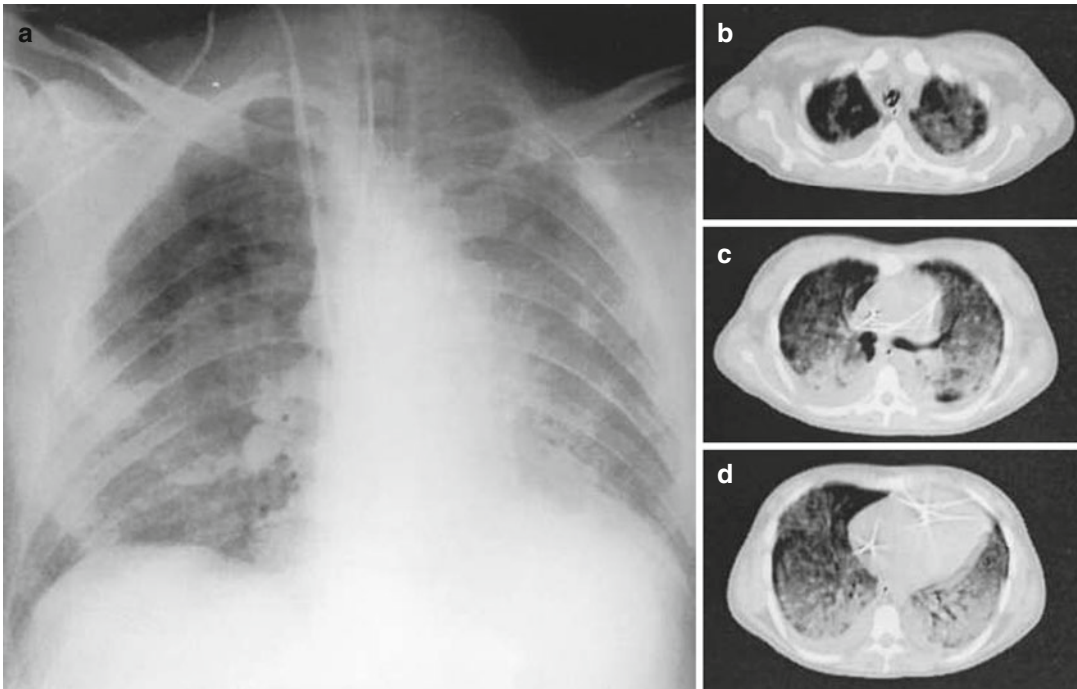


Fig. 14.9 Inhomogeneity of lung densities in acute respiratory distress syndrome. Anteroposterior chest X-ray (panel **a**) and axial CT scans at the level of the apex (**b**), hilum (**c**) and base (**d**) in a ventilated adult with acute respiratory distress syndrome from sepsis. Images were taken at a PEEP of 5 cm H₂O. The chest X-ray shows rela-

tively diffuse opacification, sparing the right upper lung. The CT scans show inhomogeneous disease in both the craniocaudal and sternovertebral gradients (Reproduced from Gattinoni et al. (2001) with permission of the American Thoracic Society. Copyright © American Thoracic Society)

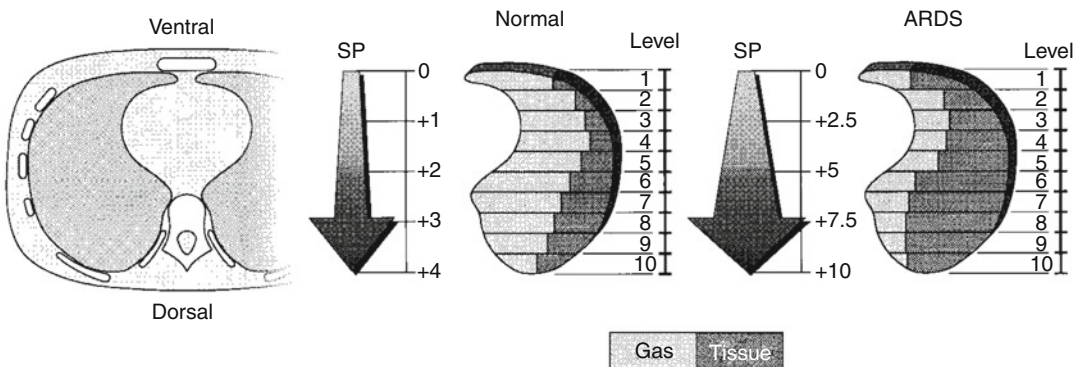


Fig. 14.10 The gradient of superimposed pressure. Increased mass of diseased lung (at *right*) causes in increased superimposed pressure, which, in turn, leads to a “gas squeezing” from the most dependent lung regions.

Superimposed pressure is expressed as cm H₂O (Reproduced from Gattinoni et al. (2001) with permission of the American Thoracic Society. Copyright © American Thoracic Society)

lung (Fig. 14.10). CT imaging has shown that dependent atelectasis occurs in the normal lung under anaesthesia (Brismar et al. 1985) and can be identified in the full-term newborn with pan-alveolar disease (Fig. 14.11). Lung regions affected by dependent atelectasis are potentially

recruitable with ventilatory manoeuvres, and this form of atelectasis can be counteracted by the use of positive end-expiratory pressure (PEEP) (Gattinoni et al. 1993). For overcoming the effects of superimposed pressure in the most dependent regions, theoretical considerations

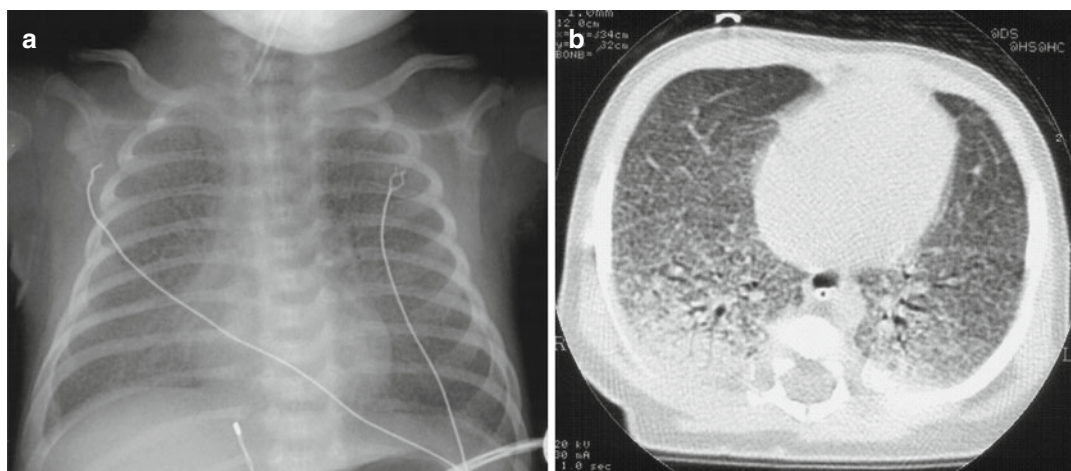


Fig. 14.11 Inhomogeneity in the ventral-dorsal axis revealed by CT scanning. Anteroposterior chest X-ray (panel **a**) and single-slice CT scan (panel **b**) from a 3-week-old ventilated infant with surfactant protein B deficiency. The chest X-ray shows diffuse reticulogranular opacification,

reflecting the pan-alveolar nature of the disease. The CT shows the inhomogeneity of lung expansion in the antero-posterior axis, with dependent atelectasis largely attributable to superimposed pressure

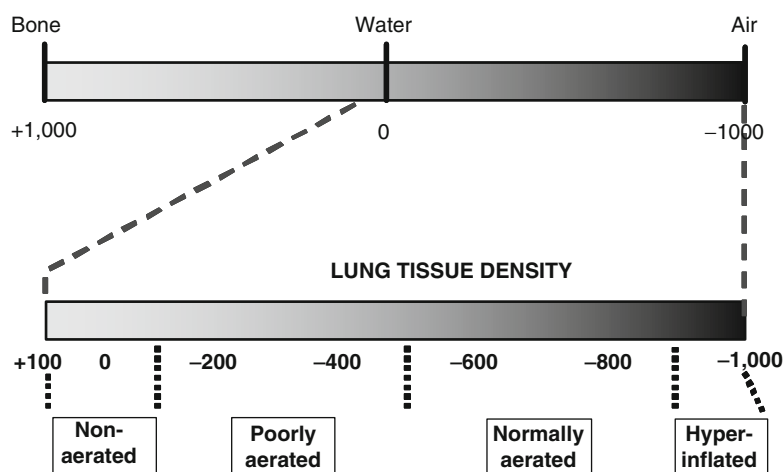


Fig. 14.12 The Hounsfield unit scale. The complete span of values from bone (+1,000) through water (0) to air (–1,000) is shown at top, and below, the range of values found in the normal and diseased lung. The lung

parenchyma in a CT slice can be identified on the basis of Hounsfield scores as being non-aerated (+100 to –100), poorly aerated (–100 to –500), normally aerated (–500 to –900) or hyperinflated (–900 to –1,000)

would suggest that a PEEP level (in cm H₂O) equivalent to the anteroposterior diameter of the chest (in cm) is required. This estimate assumes a highly diseased lung with a gas to tissue ratio close to zero (Hickling 2001).

14.2.1.2 Measurements of CT Densities

CT imaging has allowed not only delineation of the morphological pattern of pulmonary densi-

ties but also a quantitative analysis of lung aeration and its alteration during ventilatory manoeuvres. The value of CT in this regard is the use of the Hounsfield unit (HU) scale (Fig. 14.12), which allows a gas to tissue ratio and gas volume to be derived for each voxel (CT volume unit) within an axial slice and also allows the lung to be separated into aeration “compartments” (Fig. 14.12). An aeration compartment is the cumulative sum of all lung units

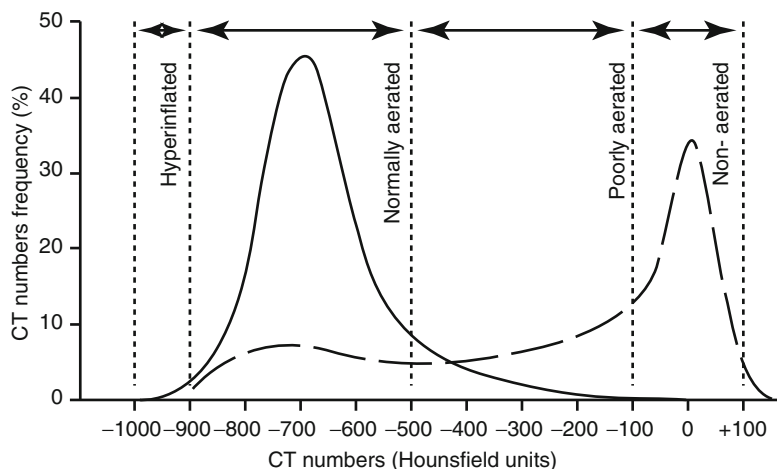


Fig. 14.13 CT histograms. Representative CT histograms from the normal lung (*solid line*) and a ventilated patient with acute respiratory distress syndrome (ARDS) (*dashed line*). Lung compartments, as defined by CT numbers, are indicated by the *dotted lines*. Note the pre-

dominance of non-aerated lung in the CT histogram in ARDS (Redrawn from Gattinoni et al. (2001) with permission of the American Thoracic Society. Copyright © American Thoracic Society)

in the CT slice having Hounsfield scores within a predefined range: non-aerated (−100 to +100 HU), poorly aerated (−100 to −500 HU), normally aerated (−500 to −900 HU) and hyperinflated (−900 to −1,000) (Gattinoni et al. 2001; Vieira et al. 1998). This information can be represented graphically in a CT histogram (Fig. 14.13), allowing the differences in aeration compartments to be highlighted in a normal and diseased lung.

Quantitative CT scanning has been used to measure changes in aeration compartments with ventilatory manoeuvres (Vieira et al. 1998; Crotti et al. 2001; Pelosi et al. 2001a; Albaiceta et al. 2004; Gattinoni et al. 2006; Lu et al. 2006; Pellicano et al. 2009). From these, much information has been gained about the nature of, and potential for, lung recruitment (Crotti et al. 2001; Pelosi et al. 2001b; Caironi et al. 2010), and the distribution of opening and closing pressures of lung units have been plotted (Crotti et al. 2001; Pelosi et al. 2001b). The impact of changes in ventilatory strategy has been demonstrated, including both the resolution of atelectasis at higher PEEP levels (Fig. 14.14) and the potential for overdistension (Vieira et al. 1998). This information has aided considerably in the understanding of application of ventilation to the diseased lung.

14.2.1.3 Limitations of CT Scanning

CT scanning has not been used in ventilated neonatal and paediatric subjects solely for the purpose of evaluating lung aeration and recruitment potential. This is chiefly because of concerns regarding radiation exposure (Mayo et al. 2003), although, with the advent of low-dose thin-section CT, the radiation dose may be 5–10 % of that with conventional CT imaging. Other limitations are lack of availability of CT scanning time and the difficulties and risks of transfer of ventilated neonatal and paediatric subjects to the CT scanning suite. For these reasons, it is unlikely that CT imaging will become widely used as a tool for evaluating regional lung inflation in this group. As discussed elsewhere in this text, there is potential for electrical impedance tomography to give similar information at the bedside of a ventilated subject, and experience with this form of imaging is growing (Frerichs et al. 2001a).

14.2.2 Magnetic Resonance Imaging

The use of magnetic resonance (MR) imaging of the lung parenchyma is essentially limited to quantification of lung water content and its spa-

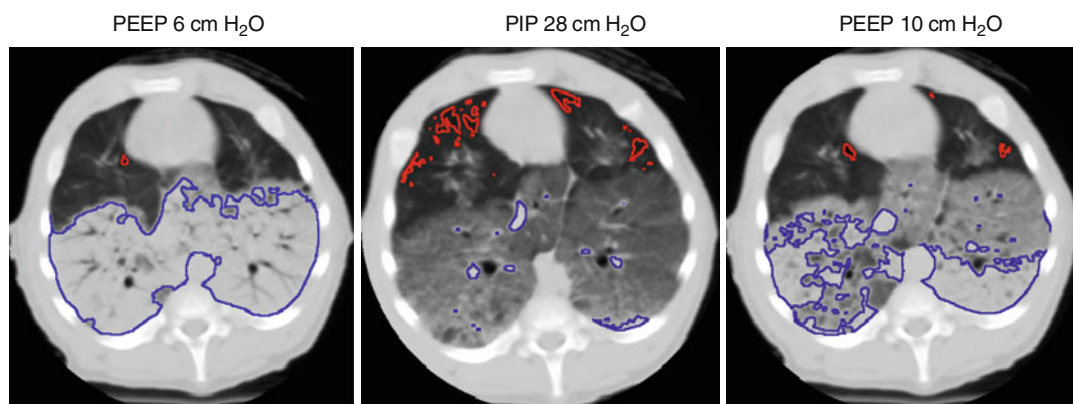


Fig. 14.14 Extremes of regional aeration during mechanical ventilation. Supra-diaphragmatic axial CT images in a 5 kg piglet with lung injury after repeated saline lavage. Areas of non-aerated lung (+100 to -100 HU) are traced in blue, and areas of hyperinflation (-900 to -1,000 HU) in red. At a PEEP of 6 cm H₂O, 53 % of the voxels are non-aerated, and only 0.15 % are

hyperinflated. After a tidal inflation to a PIP of 28 cm H₂O, very little non-aerated lung remains (2 %), but there is demonstrably more hyperinflation (2.5 % of all voxels). Ventilation with a PEEP of 10 cm H₂O results in considerable improvement in end-expiratory collapse (22 % non-aerated), with minimal effect on hyperinflation (0.43 %)

tial distribution, using proton density-weighted images. Given the relative lack of fat and other hydrogen-bound complexes in the lung, there is a direct relationship between proton density and lung water content. Studies in experimental animals (Schmidt et al. 1986; Viard et al. 2008), as well as human adults (Mayo et al. 1995) and preterm infants (Adams et al. 2002), have confirmed that MR imaging can quantify the water content of the lung and indicate its distribution. A measurable increase in water content has been demonstrated in animals with experimental pulmonary oedema (Schmidt et al. 1986). Gravity-related maldistribution of lung water, with higher water content in the dependent regions, has been observed on MR imaging (Adams et al. 2002). Clearance of lung liquid after birth has been measured in preterm lambs using the technique (Viard et al. 2008).

A single report from a neonatal unit with an onsite MR imaging suite has provided information on the lung water content and distribution in the term and preterm newborn (Adams et al. 2002). The lungs of preterm infants showed considerably greater water content than their term counterparts and a more obvious sternovertebral gradient in water distribution (Fig. 14.15). Rapid redistribution of the density gradient occurred after turning prone, and lung water appeared to

be more uniform in prone position than when supine (Adams et al. 2002).

Another application of MR imaging, not previously used in ventilated infants or children, is the use of hyperpolarised helium (³He) as a means both of tracking distribution of ventilation (Rudolph et al. 2009) and, intriguingly, of measuring intrapulmonary oxygen concentration (Eberle et al. 1999). Access to high-grade ³He gas and the gas delivery device required to control its administration are limiting factors to the wider application of this technique.

The limited availability of MR facilities, along with the need for non-ferrous ventilators and monitoring equipment, means that MR imaging is unlikely to become more widely used in the future for evaluation of either lung water content or ventilation distribution in neonatal and paediatric subjects on ventilatory support.

14.2.3 Positron Emission Tomography

Positron emission tomography (PET) is a three-dimensional functional imaging technique often combined with CT, which is based around detection of gamma radiation from a positron-emitting radionuclide. In the clinical setting, PET

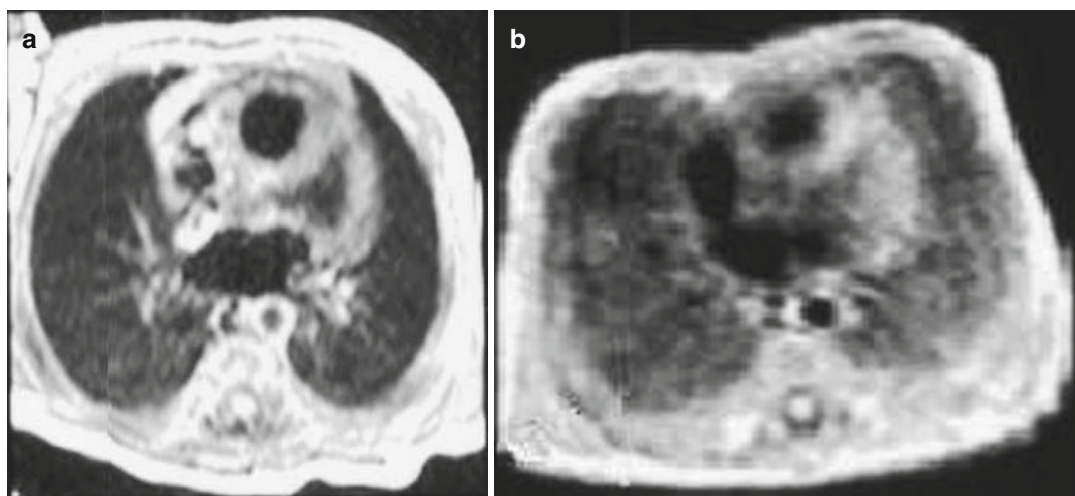


Fig. 14.15 Magnetic resonance images of the term and preterm lung. Cross-sectional T1-weighted magnetic resonance images at the level of the left atrium in a healthy term infant (panel **a**) and 26-week gestation infants at day 4 of life (panel **b**). Signal intensity in the lung parenchyma is higher in the preterm infant, with a more obvious

anteroposterior gradient of increasing signal intensity, representative of increased parenchymal water content in the dependent lung regions (Redrawn from Adams et al. (2002) with permission of the American Thoracic Society. Copyright © American Thoracic Society)

scanning is used quite extensively for diagnostic imaging of suspected pulmonary malignancy. In the research laboratory, PET techniques have been applied in experimental animals for the estimation of regional lung perfusion and water content (Schuster and Howard 1994; Richard et al. 2002) and for the evaluation of pulmonary inflammation and ventilator-induced lung injury (Kirpalani et al. 1997; Monkman et al. 2004; Costa et al. 2010). These latter studies used ^{18}F fluorodeoxyglucose, a tracer that is taken up into neutrophils and thus preferentially localises in areas of inflammation, including in the lung parenchyma. In newborn piglets, a clear increase in tracer uptake by the lung has been noted after injurious ventilation compared to controls with normal lungs (Kirpalani et al. 1997). Increased tracer uptake was seen in ventilated sheep with endotoxaemia to be localised to regions that were both aerated and perfused (Costa et al. 2010), suggesting that factors beyond gas distribution alone contribute to regional neutrophilic inflammation during lung injury with associated endotoxaemia.

A single investigative group has examined the possibility that PET scanning could discern differences in lung inflammation in preterm infants with and without exposure to inflammation prenatally

(Andersen et al. 2003). No clear differences in ^{18}F FDG uptake were observed in preterm infants with a history of maternal chorioamnionitis compared with those with no antenatal inflammation. Several infants with no apparent systemic inflammatory response had very high tracer uptake in the lung on PET scanning (Andersen et al. 2003). This study did not point to a potential role for PET scanning in the investigation of lung inflammation in the ventilated preterm infant, and no further studies have been forthcoming.

Essentials to Remember

- CT imaging of the diseased lung has revealed the heterogeneity of parenchymal densities, related both to random distributional effects and to gravity-related compressive forces acting on dependent regions.
- CT imaging in ventilated adults with acute respiratory distress syndrome can map the distribution of opening pressures and quantify the potential for recruitment in response to sustained airway pressure.

- MR imaging and PET scanning have contributed to the understanding of lung water content and distribution of aeration, but are not currently used in the clinical setting for these applications.
- The limited availability of these imaging techniques, coupled with technical difficulties peculiar to each, precludes a recommendation for their use in the management of ventilated infants and children with lung disease.

14.3 Bedside Lung Imaging Methods (Electrical Impedance Tomography)

Inéz Frerichs

Educational Aims

- To understand the measuring principle of EIT
- To learn how EIT is able to track changes in regional lung volumes and tidal volume distribution as well as to determine regional dynamic phenomena in lung ventilation
- To identify the potential benefit of functional EIT lung imaging in monitoring of ventilated neonatal and paediatric patients
- To identify the present limitations and drawbacks of EIT

14.3.1 Introduction

The use of established radiological imaging methods in respiratory monitoring of mechanically ventilated infants is limited especially because of the imposed radiation load or the necessity of patient transport to the examination site. Ventilated patients would benefit from new monitoring approaches providing instantaneous

assessment of regional lung function at the bedside and enabling more rapid adjustment of ventilator settings. The non-invasive and radiation-free method of electrical impedance tomography (EIT) has recently been proposed as a possible future monitoring tool in this indication. EIT allows the assessment of regional lung ventilation and of changes in regional lung volumes based on the measurement of electrical properties of the lung tissue. EIT has no known hazards and can be applied at the bedside. However, EIT has not been used routinely in a clinical setting, thus, its usefulness still has to be proved. Several small clinical studies in neonatal and paediatric patients indicate the potential of EIT monitoring. To establish the method as a routine medical examination tool, further development of the EIT hardware and software is necessary. Definition of the most adequate EIT examination procedures providing measures suitable for clinical decision-making and optimising the ventilator therapy is the other prerequisite.

14.3.2 Technique

14.3.2.1 Electrical Bioimpedance

The idea of imaging the human body by electrical current is not new. It is based on the fact that the tissue electrical properties are not uniform and vary among different organs (Geddes and Baker 1967). Biological tissues can conduct electrical current; however, their opposition to the transmission of current is not the same.

In general terms, any opposition of a medium to transmission of a time-varying signal is called impedance. If this medium is a biological tissue, then we speak of bioimpedance. If the time-varying signal used to probe the biological tissue is alternating electrical current, then the term electrical bioimpedance is used. The measurement of electrical bioimpedance is already being utilised by a few medical technologies (Table 14.2). In electrical impedance tomography (EIT), images of the distribution of electrical bioimpedance within the body are generated.

Table 14.2 Medical examination techniques based on the measurement of electrical bioimpedance

Method	Main information retrieved
Bioimpedance analysis	Body composition
Impedance cardiography	Cardiac output
Impedance pneumography	Respiratory rate
Impedance tomography	Body imaging

The first attempts to produce electrical bioimpedance images of the body originate already from the late 1970s of the last century. They aimed at generating anterior to posterior chest images, similar to chest radiography (Henderson and Webster 1978). The first EIT system producing cross-sectional, i.e. tomographic images of the human body was developed by David C. Barber and Brian H. Brown in the early 1980s of the last century (Barber and Brown 1984).

14.3.2.2 EIT Setup

EIT uses a set of measurement electrodes which are attached on the surface of the studied body section. If an EIT examination is performed on the chest, then the electrodes are placed on the chest circumference usually in one transverse plane (Fig. 14.16). The electrodes either are integrated in an electrode band or are individually attached on the thorax wall. In the latter case, conventional self-adhesive ECG electrodes may be used. The use of X-ray translucent electrodes is also possible. The electrodes are connected with the EIT device by leads.

Most of the currently used EIT systems use an array of 16 electrodes. This number of electrodes is a good compromise securing sufficient image resolution and equidistant placement of electrodes without the risk of undesirable accidental electrode contact. Eight- and thirty-two-electrode EIT systems have also been developed; however, the loss in spatial resolution or the necessity of placing a large number of electrodes on the chest makes these systems less adequate.

14.3.2.3 EIT Data Acquisition

During an EIT examination, minute alternating electrical currents are injected into the body. These currents have an amplitude of only a few

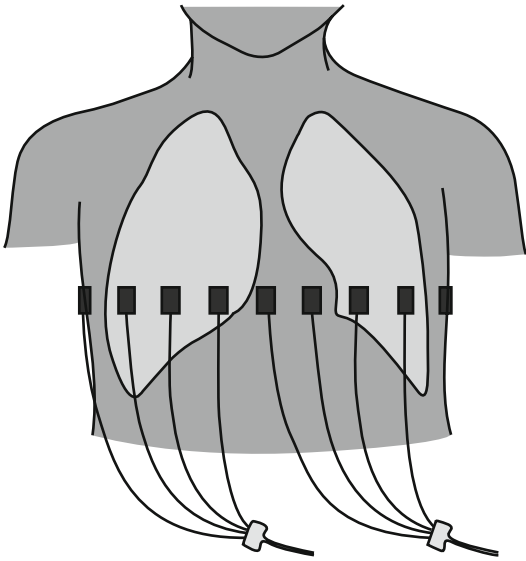


Fig. 14.16 Measuring principle of EIT. An array of surface electrodes is attached on the chest circumference in one transverse plane and connected via leads with the EIT device. Very small alternating electrical currents are consecutively applied through all adjacent pairs of electrodes. The resulting potential differences are measured at all passive electrode pairs during each current application. The process of current applications and acquisitions of potential differences rotates around the chest at high rates

mA and a frequency in the range of approximately 10 kHz–1 MHz. The currents are applied between adjacent pairs of electrodes in most of the EIT systems. The current-carrying electrode pairs are cyclically activated, and the current injection rotates around the body. During each application of electrical current, the resulting potential differences are measured between all other passive electrode pairs. The voltage distribution developed on the surface of the chest is determined by the internal distribution of electrical resistances within the chest and its shape. Also in the case of voltage measurement, adjacent electrodes are preferentially used. With the described 16-electrode arrangement and pattern of rotating current application and voltage measurement, a total of 208 voltage values are acquired during each scan cycle. The maximum EIT scan rate is rather high. With up to 50–60 scans/s, it is much higher than in other, classical radiological tomographic methods, like computed tomography or magnetic resonance imaging.

14.3.2.4 EIT Image Reconstruction

The set of electrical voltages acquired at the chest surface as a result of electrical current application during each scan cycle is used to calculate the distribution of electrical impedance within the thorax. The calculated impedance values are then converted to a two-dimensional, cross-sectional EIT scan in an either grey or colour scale. This process of generation of impedance distribution images from the measured potential differences and known excitation currents is called image reconstruction (Barber 1990; Morucci and Marsili 1996).

The generation of EIT scans is not easy. This is first of all related to the fact that the human body is a three-dimensional object. Electrical currents applied through the electrodes at the boundary of the chest are not confined to the two-dimensional transverse plane, defined by the electrode array. The currents also flow into more distant regions, and their pathways are not known. This means that EIT scans always reflect not only the impedance distribution in the studied plane but are also affected by tissues lying outside of the measurement plane, although with lower sensitivity. Another point is that the currents tend to penetrate less into the deeper chest regions. Therefore, the spatial resolution also tends to be poorer in the centre than at the chest periphery.

In general, there exist three major ways how EIT scans can be generated (Boone et al. 1997). The first approach aims at depicting the distribution of absolute values of electrical impedance within the chest. Although such images have already been obtained *in vivo*, their quality was rather poor. This is mainly because these images are very sensitive to EIT data collection errors and require the knowledge of the shape of the body. The same limitations also apply to the second approach, which tries to differentiate the tissues based on their varying response to electrical currents of different frequencies. The most frequently used approach is the third one, in which changes or differences in electrical impedance are determined and converted to EIT scans. The advantages of this approach are that errors tend to cancel and the uncertainties about the body shape do not affect the image quality. The calculated

impedance changes are often normalised by relating them to a reference state of impedance. This is, for instance, done when the so-called weighted backprojection (Barber 1990) is used, which has been the most often used method of EIT image reconstruction in *in vivo* EIT imaging so far. All EIT scans shown in the figures in this chapter have been generated using this type of image reconstruction.

The weighted backprojection algorithm is a rather old approach to image reconstruction known to be associated with several assumptions which are not met during measurements in humans. Nevertheless, it has been successfully applied in multiple clinical studies. Several other EIT image reconstruction algorithms have been developed over the past 20 years; however, their performance has mostly been tested only under *in vitro* conditions. EIT image reconstruction is one of the most active fields in EIT research. Only recently, an initiative of a large and representative group of experts has been formed to develop a unified reconstruction algorithm for lung EIT imaging which should secure the highest possible and uniform spatial resolution, accuracy and sensitivity (Adler et al. 2009).

14.3.3 Image Interpretation and Qualitative Analysis

An EIT chest examination results in a series of EIT scans acquired during a selected period of time (Fig. 14.17). In ventilated patients, these scans usually cover a period of multiple breaths, a ventilation manoeuvre (for instance, a pressure-volume manoeuvre, suctioning) or another intervention (change in ventilator settings or mode).

Such series of individual EIT scans can be displayed directly online during the data acquisition or offline after the completion of the examination. Thanks to the high EIT scan rates, they result in a video sequence of the instantaneous distributions of electrical impedance in the chest. Such videos are dominated by the large impedance changes associated with the variation in regional lung volume; the much smaller changes in the cardiac region are often also discernible.

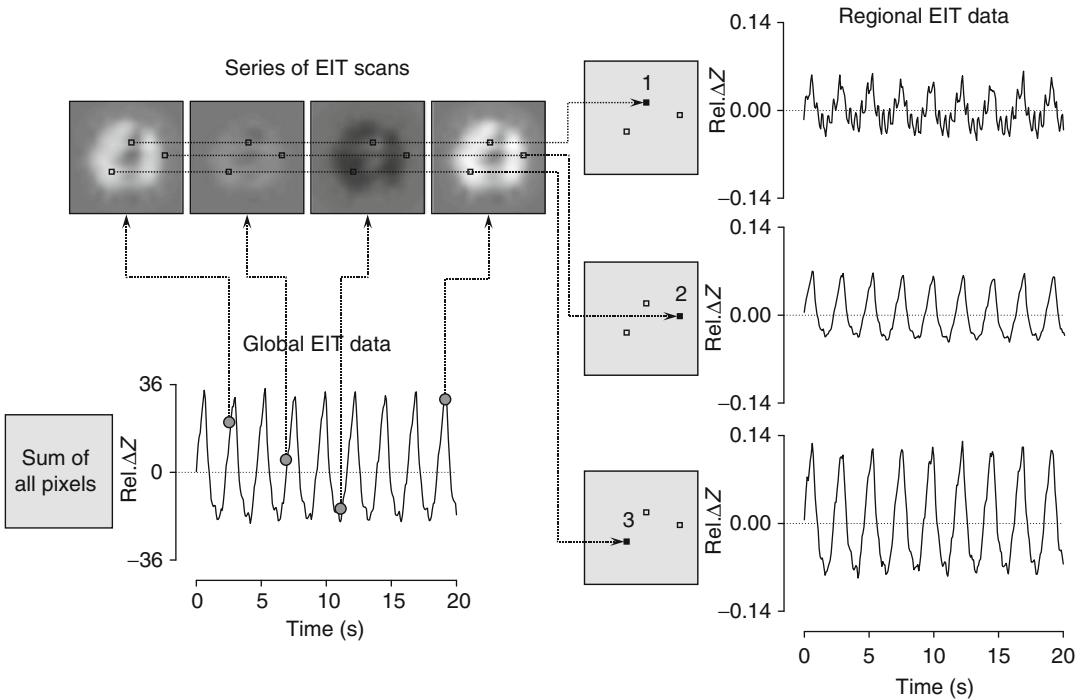


Fig. 14.17 Chest EIT scans and regional EIT tracings. During an EIT examination, a series of EIT scans is acquired showing the instantaneous distribution of electrical impedance changes in the chest cross-section relative to a reference state (*top left*). In this example, the reference impedance distribution corresponded to the average impedance distribution during a 20-s long phase of mechanical ventilation. Thus, the EIT scans show higher regional impedance values at higher regional lung volumes (*light tones*), lower values at lower volumes (*dark tones*) or minimum changes when the regional lung volumes were close to the reference volumes. The tracing of global EIT data (*bottom left*) was generated by summing up all 912 image pixel values of relative impedance change ($\text{rel.}\Delta Z$) in each scan of the acquired series and plotting them as a function of time. An increase in impedance values occurs during inspiration, a fall in impedance is observed during expiration. The light grey circles and the dotted arrows indicate at which moment of the respiratory cycle; the four EIT scans were obtained. The tracings of regional EIT data (*right*) originate from three image

pixels shown as small squares in the EIT scans. The *top* tracing is a plot of a time series of local relative impedance change obtained in pixel 1 which was located in an anterior region of the chest. Thus, the signal contains impedance changes related to ventilation superimposed on which are the more frequent changes synchronous with the heart rate. The *middle* tracing originates from the pixel 2 located at the edge of the left lung region showing predominantly the ventilation-related impedance changes. The *bottom* tracing was obtained in the pixel 3 in the right lung region and shows the highest ventilation-related changes in impedance with time. (The EIT data presented in this figure originate from an EIT examination of an 8-week-old infant with a body weight of 4,585 g and a length of 56 cm. The infant suffered from posthaemorrhagic hydrocephalus and was studied in the operating room prior to surgery during continuous positive pressure ventilation with a tidal volume of 10 mL/kg body weight and positive end-expiratory pressure of 4 cm H₂O. The respiratory rate was 26 breaths/min, the inspiration/expiration ratio was 1/1 and the fraction of inspired O₂ 23 %)

The even smaller cyclic EIT signal variation caused by lung perfusion is usually masked by the large impedance changes during ventilation. Thus, lung perfusion only becomes visible in such video sequences when the lung air content does not change, e.g. during apnoea. The series of individual EIT scans are usually considered only the first step in further evaluation.

EIT can track rapid regional changes in electrical impedance in the chest cross-section resulting from the physiological processes like ventilation, heart action or lung perfusion. Figure 14.17 illustrates this capability of EIT by showing the regional tracings of EIT data in three image pixels. These tracings reveal the typical ventilation-related variation of the EIT signal as well as the

heart beat synchronous variation detectable especially in the heart region. The excellent time resolution of EIT with high scan rates allows even more frequent events to be tracked, like the very small and rapid air volume oscillations during high-frequency oscillation ventilation.

Thus, the regional pixel tracings of EIT data contain valuable compressed information on different aspects of the lung function which can be addressed and evaluated using various functional evaluation approaches. Functional EIT imaging allows the generation of the so-called functional EIT scans from the series of individual EIT scans which provide condensed and separate information on one selected aspect of the lung function, e.g. the spatial distribution of lung volume changes or tidal volumes, as will be described in the next text section. A series of individual EIT scans containing hundreds or even thousands of scans may serve as a basis for generation of several types of functional EIT scans. For instance, the functional EIT scan in Fig. 14.18 was generated from the 20-s series of 500 EIT scans shown

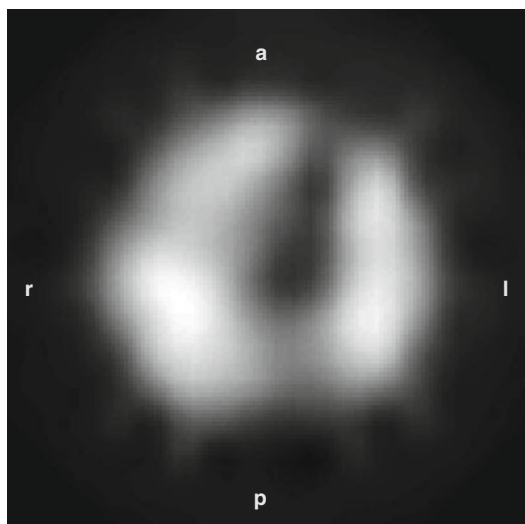


Fig. 14.18 Functional EIT scan showing the distribution of tidal volume in the chest cross-section. This scan was generated from the same EIT examination presented in Fig. 14.17 by calculating the average regional tidal, i.e. inspiratory to expiratory difference in electrical impedance in each image pixel during 20 s of mechanical ventilation. The spatial orientation of the scan is indicated (*a* anterior, *p* posterior, *r* right, *l* left)

in Fig. 14.17 and characterises the ventilation distribution in the chest cross section during this EIT examination.

14.3.4 Tracking Lung Volumes and Tidal Volume Distribution

14.3.4.1 Changes in Regional Lung Volumes

The ability of EIT to track regional lung volume changes has been validated by several established imaging modalities (computed tomography, positron emission tomography, single-photon emission computed tomography, ventilation scintigraphy) (Frerichs et al. 2002; Hinz et al. 2003b; Kunst et al. 1998; Richard et al. 2009; Serrano et al. 2002; Victorino et al. 2004; Wrigge et al. 2008) and other medical methods (spirometry, inert gas washout) (Hahn et al. 1995; Harris et al. 1987; Hinz et al. 2003a).

An increase in the lung air content leading to a rise in lung volume is accompanied by an increase in electrical impedance. Electrical impedance falls when lung volume decreases. These typical impedance changes occur regularly during the respiratory cycle both during spontaneous breathing or mechanical ventilation. In ventilated patients, additional lung volume changes may result from altered ventilator settings.

Changes in positive end-expiratory pressure (PEEP) influence the aeration of the lungs and, consequently, the impedance level, on which the cyclic ventilation-related variation of the EIT signal is superimposed (Erlandsson et al. 2006; Frerichs et al. 1999a, 2003a; Meier et al. 2008). The changes in aeration may be spatially inhomogeneous, and it is the advantage of EIT that it can track these aeration changes on a regional level. For instance, an increase in regional electrical impedance in the dependent lung regions after an increase in PEEP may indicate alveolar recruitment. Merely a small increase in impedance in the nondependent regions with a pronounced effect in other regions may hint at possible local overdistension.

Figure 14.19 illustrates the potential of EIT in tracking regional lung volumes in another exam-

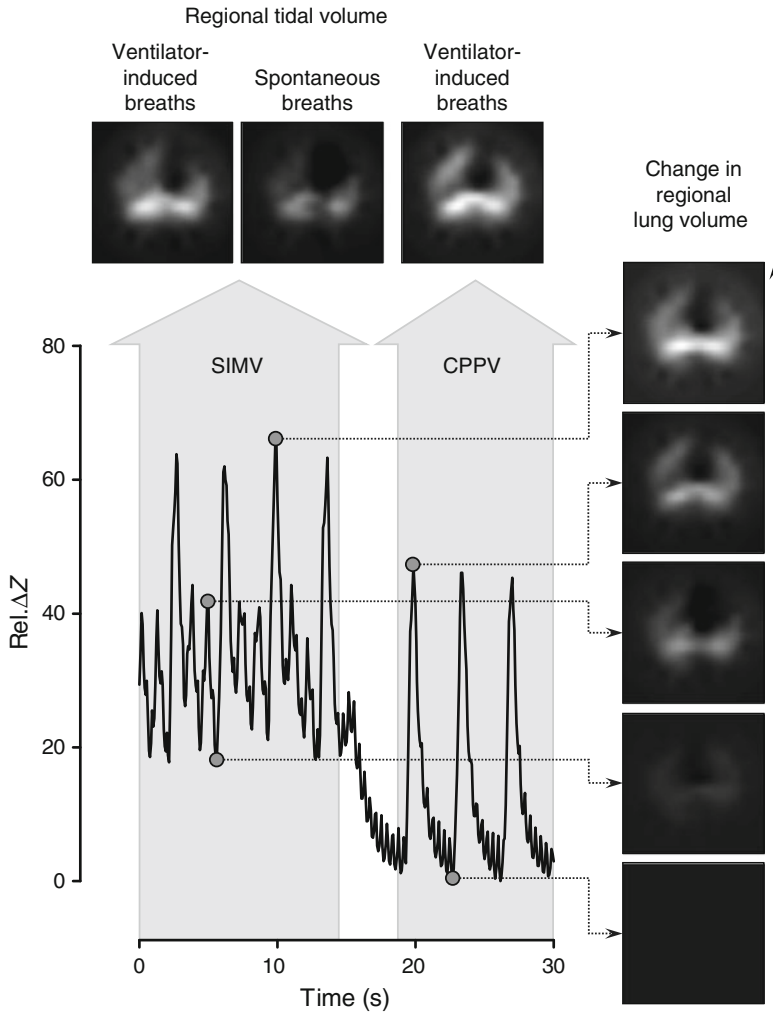


Fig. 14.19 EIT examination during weaning from mechanical ventilation. A 30-s tracing of global EIT data is shown, generated by summing up all 912 EIT image pixel values of relative impedance change ($\text{rel.}\Delta Z$) from a series of 750 EIT scans. The examination was performed in a 10-week-old preterm infant with a body weight of 2,500 g and a length of 44 cm. The data was acquired in a neonatal intensive care unit during postoperative weaning from mechanical ventilation after orchiopexy. The infant was ventilated in an assisted mode with synchronised intermittent mandatory ventilation (SIMV). The respiratory rate was 16 breaths/min, the inspiration/expiration ratio was 1/5.2, positive end-expiratory pressure 3 cm H₂O, peak inspiratory pressure 24 cm H₂O and the fraction of inspired O₂ 21 %. During the initial phase of the examination, highlighted by the first light grey area, the EIT signal reflects the typical lung volume changes occurring in the lungs during SIMV: the four large deflections represent the larger ventilator-induced breaths, the smaller deflections in between originate from the smaller

spontaneous tidal breaths. During the subsequent short apnoea, the impedance values fall to a new end-expiratory level due to loss in lung volume, followed by three-controlled ventilator-induced breaths during continuous positive pressure ventilation (CPPV), highlighted by the second light grey area. The small and rapid impedance signal fluctuations, discernible especially during the apnoeic and CPPV phases, are synchronous with the heart rate of 152 beats/min. The three images at the top of the figure are functional EIT scans showing the distribution of tidal volumes: the left two of these scans were generated from the SIMV phase and provide the distribution of both ventilator-induced and spontaneous breaths, and the right image shows the tidal volume distribution during CPPV. Of note is the more pronounced ventilation of anterior lung regions during fully controlled ventilation without spontaneous breathing activity. The five functional scans on the right show the changes in regional lung volume at different phases of the EIT examination compared with the lowest volume at end-expiration during CPPV

ple. This EIT examination was performed in a ventilated infant during weaning and shows the loss in lung volume after temporary cessation of spontaneous breathing activity during assisted ventilation. The lowest level of lung aeration was noted at end-expiration after the spontaneous breathing had ceased. Functional EIT scans can be generated which visualise the instantaneous level of aeration at different time points of the examination.

14.3.4.2 Tidal Volume Distribution

During tidal spontaneous or artificial ventilation, the highest values of electrical impedance occur at end-inspiration, the lowest at end-expiration. The differences between the regional peak and trough values of the EIT signal are representative of regional tidal volumes. If these regional differences between the maximum and minimum impedance values are calculated from one or more respiratory cycles in each image pixel, they may be converted in another type of a functional EIT scan showing the distribution of tidal volume in the chest cross-section.

The distribution of tidal volume is influenced by the type of ventilation (spontaneous vs. mechanical), body position and gravity and by the local mechanical properties of the lung tissue which may be nonhomogeneously altered by lung pathology. Figure 14.19 shows how the tidal volume distribution may vary even within a very short time interval. In the course of this EIT examination, which was already referred to in the above text, the studied infant was ventilated in an assisted mode of ventilation. Ventilation was accomplished by ventilator-induced breaths in combination with spontaneous breathing activity. The functional EIT scans of tidal volume distribution generated from this phase of the EIT examination show that the regional tidal volumes were smaller during the spontaneous than ventilator-induced breaths; nevertheless, their spatial distribution was similar. An interesting phenomenon is revealed when the distribution of the ventilator-induced tidal volumes is compared between this phase and the phase when the infant ceased to breathe spontaneously. A more pro-

nounced distribution of the tidal volume to the nondependent anterior regions was found in the latter phase indicating that a spatial redistribution of tidal volume had occurred when the mechanical breaths were applied at a lower end-expiratory lung volume.

14.3.4.3 Combination of Functional EIT Information

It was explained in the above text that functional EIT scans of various types can be generated from the same EIT examination by application of various evaluation steps and procedures. Figure 14.19 provided an example in which functional EIT scans showing the tidal volume distribution and regional lung volume changes relative to the lowest end-expiratory volume were obtained from the same EIT data by different analysis. The interpretation of multiple functional EIT scans may offer a deeper insight into the regional lung function. Even more detailed understanding could be obtained if functional EIT information is extracted from examinations performed during predefined manoeuvres, for instance, during a PEEP trial (Frerichs et al. 2003a; Meier et al. 2008).

The high scan rates achievable during EIT examinations allow an assessment of rapid dynamic phenomena in the regional lung function. Therefore, not only the above-mentioned regional lung volume changes and tidal volumes can be measured but also the dynamics of regional lung filling and emptying described (Frerichs et al. 2001b). For instance, progressive filling of lung regions characterised by an increasing rate of impedance change may occur during tidal lung recruitment or degressive filling with a decreasing rate of impedance change may arise from overinflation (Hinz et al. 2007). A regional time delay in an increase in impedance during lung inflation (Wrigge et al. 2008) may be a sign of airway collapse with delayed opening of the affected lung units. Regional tracings of the EIT signal registered after a stepwise change in airway pressure may be used to calculate the distribution of regional time constants.

Since many of the physiological processes in the lungs like ventilation and cardiac action,

which contribute to the time variation of the EIT signal, are of cyclic origin, they can be separated by using frequency filtering procedures (Dunlop et al. 2006; Frerichs et al. 2001a, 2009). Independent analysis of these processes is then possible. For instance, the functional EIT scans of tidal volume distribution during ventilator-induced and spontaneous breaths during assisted ventilation shown in Fig. 14.19 could easily be generated because the ventilator and spontaneous breathing rates were not equal.

Thus, a variety of information on different aspects of regional lung function can be obtained from EIT examinations (Bodenstein et al. 2009; Brown 2003; Costa et al. 2009; Frerichs 2000). There exist two ways how this information can be used in clinical decision-making: (1) It can be visualised in form of functional EIT scans. This way of presentation is suitable if rapid information on the spatial distribution of a chosen relevant lung function measure is needed. (2) Alternatively, the relevant EIT lung function measure can be calculated in meaningful pulmonary regions of interest (Pulletz et al. 2008; Victorino et al. 2004; Zhao et al. 2009) and used in its numeric form, for instance, to follow regional changes in lung function over time. EIT data are then acquired during a longer monitoring interval or as a series of short but repetitive examinations. This approach may be applied, for example, to establish if a recruitment manoeuvre or a change in ventilator settings opened an atelectatic region with a non-transient effect on regional tidal volume.

14.3.5 Clinical Experience

Clinical experience with EIT use for lung imaging in neonatal and paediatric patients is scarce. Until 2009, less than 20 EIT studies have been conducted in this patient group, mostly in rather small numbers of patients. The number of experimental and clinical studies in adults is much higher. Many of these studies possess a high degree of relevance for EIT application in the neonatal/paediatric field.

EIT studies in neonates and infants have mostly been motivated by two goals. The first one

was to utilise the full non-invasiveness and lack of radiation of this new examination method to study such phenomena in the lung function which were previously not accessible to other established medical modalities or not ethically justified. EIT enabled regional analysis of lung function in pre-term infants or neonates. Even lung healthy babies could be examined by EIT during undisturbed spontaneous breathing. Since very little is known about the regional lung function in patients of this age group, EIT was able to provide valuable information on the ventilation distribution under a variety of conditions. For instance, the significant effects of body and head position and the influence of the respiratory pattern (e.g. respiratory rate, sighs) on the spatial distribution of ventilation were established (Frerichs et al. 2003b; Heinrich et al. 2006). Furthermore, the differences in regional ventilation between preterm and term neonates could be addressed (Riedel et al. 2009). The specific features of the neonatal ventilation distribution pattern have been studied and compared with adults (Dunlop et al. 2006; Schibler et al. 2009; Smallwood et al. 1999). A few studies have been performed in neonates with the aim of determining the effect of maturational changes on the lung electrical properties, showing that increased alveolisation is associated with higher electrical impedance of the lung tissue (Brown et al. 2002a, b).

The other studies were motivated by the awareness of the potential of EIT in monitoring ventilated infants. EIT was applied to determine the effects of changed ventilator settings or therapeutic procedures (surfactant administration, suctioning) on regional lung function. These studies were performed in neonatal and paediatric intensive care units and provided the first evidence that useful feedback information can be generated by EIT at the bedside. The studied infant patients were followed by EIT during spontaneous breathing and different modes of mechanical ventilation (e.g. non-invasive and invasive ventilation in fully controlled conventional and high-frequency oscillation modes or assisted ventilation). It has been demonstrated that the immediate effects of changing PEEP, peak inspiratory pressure, inspiration-to-expiration time ratio and fraction

of inspired O_2 on the spatial distribution of ventilation were discernible (Frerichs et al. 2001a). Long-term monitoring of several days duration was also successfully accomplished to study regional lung ventilation in a critically ill neonate before and after cardiac surgery (Frerichs et al. 1999b). It has also been shown that rapid, regionally heterogeneous derecruitment induced by suctioning can be detected by EIT in children suffering from ARDS (Wolf et al. 2007). Finally, regional end-expiratory lung volumes were determined by EIT in ventilated infants with respiratory failure due to a respiratory syncytial virus infection (Kneyber et al. 2009).

14.3.6 Limitations and Drawbacks

Although EIT certainly exhibits many features which make this medical technology interesting for monitoring regional lung function in neonatal and paediatric patients, it is too early to say whether it will be able to prove its applicability and value in a routine clinical setting. Table 14.3 summarises the pros and cons of EIT imaging from the today's point of view.

With a clear lack of other alternative medical modalities suitable for monitoring regional lung function in ventilated infants at the bedside EIT possesses many intriguing characteristics: It allows continuous measurement of regional lung volumes and tidal volume distribution as well as the assessment of other regional measures characterising the dynamics of lung behaviour during mechanical but also spontaneous breathing. To obtain this kind of information, no radiation exposure is necessary; there exist no known hazards. After the application of EIT electrodes on the chest, continuous EIT scanning can easily be performed and interrupted any time.

The disadvantages of EIT comprise first of all the relatively low spatial resolution of EIT scans. Although continuous technological development and use of more advanced image reconstruction procedures can be expected to improve the EIT image quality, image resolutions as known in conventional chest radiography, computed tomography and magnetic resonance imaging

Table 14.3 Pros and cons of EIT lung imaging

Advantages	Disadvantages
Non-invasiveness, no exposure to radiation, no known hazard	Poor spatial resolution
Low price	Necessity of surface electrodes or electrode bands
Small size, portability, bedside application	Hardware and software not yet optimised for clinical routine
Generation of tomographic images of a new biological quality	Procedures and quantitative parameters for clinical decision-making not yet defined
Good temporal resolution (i.e. high scan rate)	Large clinical studies lacking
Continuous examination (i.e. monitoring)	
Functional imaging	

will never be possible (Seagar et al. 1987). However, it has to be pointed out that EIT is not intended to be recommended as a sole imaging method. A meaningful combination of patient examinations using conventional imaging modalities, providing excellent anatomical information, and EIT, providing functional information, should be aspired. The conventional methods will make intermittent information on lung morphology available; EIT will offer continuous monitoring of lung function.

The essential drawback of EIT at present is that it has hardly been applied in large clinical trials. The final proof of clinical relevance and efficacy is still lacking. Many of the intriguing data obtained by this method in ventilated neonates and infants were merely small observational studies, in part, simple case reports. This means that EIT must be applied in larger groups of patients with clearly defined goals and outcome measures. One of the most important objectives should be the definition of appropriate procedures for standardised EIT examination of patients. Such procedures should provide relevant EIT measures suitable for clinical decision-making and optimisation of ventilator therapy. Since EIT has the perspective of becoming a broadly used monitoring tool at the bedside, it will be operated by the medical personnel and not

only by a few specialists, as is the case today. Therefore, factors like practicability of application and user friendliness of EIT data acquisition and evaluation will also play an important role in the clinical implementation of this technology.

14.3.7 Perspectives

EIT has the potential of becoming a bedside monitoring tool for monitoring regional lung function in ventilated neonatal and paediatric patients. This perspective is based on (1) the clinical need for improved patient monitoring, (2) several positive characteristics of this technology which are superior to other existing imaging modalities and (3) promising findings of hitherto existing EIT studies. The present interest in EIT is mainly driven by the increasing knowledge of possible detrimental effects of mechanical ventilation. If EIT monitoring succeeds to be established in a clinical setting, then it may provide online feedback on regional lung function and its changes in response to modified ventilator settings and other therapeutic procedures. This may facilitate individually optimised mechanical ventilation and minimise the incidence of ventilator-induced lung injury.

Essentials to Remember

- EIT is a non-invasive, radiation-free bedside medical imaging modality.
- EIT generates cross-sectional images of distribution of electrical bioimpedance within the chest.
- EIT allows functional lung imaging, thanks to very high scan rates.
- Functional EIT is able to determine changes in regional lung volumes and tidal volume distribution as well as regional dynamic phenomena in lung ventilation.
- Ventilated patients may benefit from future EIT monitoring since an immediate feedback on regional lung function may facilitate rapid adjustment of ventilator settings.

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Monitoring Interactions Between Spontaneous Respiration and Mechanical Inflations

15

Mark Heulitt and Steven M. Donn

Education Aims

- Understand the relationship between the two controllers involved in patients breathing spontaneously on mechanical ventilation.
- Understand the phases of mechanical ventilation and the role they play in the interactions between the patient and the ventilator.
- Identify the different types of patient-ventilator asynchrony and understand their physiologic implications for the development of asynchrony.

controllers: the clinician-controlled mechanical pump (the ventilator) and the patient's own respiratory muscle pump. The interactions between these two controllers can best be described by examining Newton's equation of motion.

$$P_T = P_{\text{mus}} + P_{\text{appl}} = (V \times R_{\text{rs}}) + (V \times E_{\text{rs}})$$

The equation explains the interaction of between the patient's generated pressure, P_{mus} , and the ventilator's generated pressure, P_{appl} . These pressures overcome the resistance (R_{rs}) and elastance (E_{rs}) of the respiratory system. In this equation, inertia is negligible, especially in pediatric patients. This interaction is complex and involves numerous feedback pathways. For example, respiratory muscles are affected by the force-length and force-velocity relationship causing a mechanical feedback to the patient's motor center and spinal nerves from receptors in the airway, chest wall, or respiratory muscles; this has been described as the reflex feedback (Kondili et al. 2003). This relationship between the muscle feedback and reflex feedback is not well studied in mechanically ventilated pediatric patients, especially neonates, where the immaturity of the receptors, controllers, and muscle response may impact these relationships. The variables that can potentially impact the patient-ventilator interaction are also complex and include patient and ventilator factors and the patient's feedback system. These interactions create a response loop that is affected by this interaction between ventilator (controllers of the ventilator breath, including trigger, gas delivery, and how the

15.1 Introduction

Pediatric and neonatal patients breathe spontaneously during mechanical ventilation. This involves the combination of two distinct

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breath is terminated) and patient factors (mechanics of the respiratory system and muscular response), which cause a volume change with time, affecting the patient's muscular response, which in turn is affected by the force-muscle and force-velocity relationship of the respiratory muscles. This volume-time profile influences the patient's feedback system (chemical, mechanical, reflex, and behavioral) that then determines the muscular response of the patient's to the ventilator breath. The final influence on these interactions involves the clinician and his choice of the trigger, mode of ventilation, and level of support. Our discussion on monitoring the interaction of spontaneous respiration and mechanical inflation will focus on the identification of asynchrony between the patient controller and the ventilator.

15.2 Response of the Ventilator to Patient Effort

Factors affecting the response of the ventilator to the patient can be subdivided into the ventilator factors affecting the initiation of the breath (trigger variable), how the breath is sustained (gas control variable), and how the breath is terminated (cycle off criterion). Patient-related factors include the mechanics of the patient's respiratory system and characteristics of the patient-generated muscular response or pressure generated by the patient's respiratory muscles or P_{mus} . As can be seen in Fig. 15.1, the pressure generated when a patient is spontaneously breathing while receiving positive pressure ventilation is the sum of the pressure generated by the patient's respiratory muscles (P_{mus}) and that generated by the ventilator (P_{applied}). The proportion of each of these pressures is dependent upon the patient's respiratory drive, mechanics, and muscular response, the ventilator's trigger characteristics, and the selected ventilator mode. The mode is dependent upon the control, phase, and conditional variables. Our discussion will first focus on patient and ventilator characteristics followed by a review of when there is inability of the patient and ventilator controllers to act synchronously.

15.2.1 Ventilator-Related Factors

The response of the ventilator to a patient's effort is influenced by ventilator variables including the trigger variable that initiates the breath, pressure delivery, and the cycle variable that terminates the breath.

15.2.2 Trigger Variable

The trigger variable is controlled by either a flow or pressure signal derived from the airway. Figure 15.2 illustrates a comparison of two trigger variables. For pressure triggering, the patient must decrease the pressure in the ventilator circuit, by an isometric contraction of the respiratory muscles, to a preset value to completely open the inspiratory valve and initiate a mechanical breath. In flow triggering, the patient must generate a change in flow, sensed between the ventilator's inspiratory and expiratory pneumotachographs, by an isotonic contraction of the respiratory muscles. It has been generally believed that there are distinct advantages of flow triggering (Carmack et al. 1995; Branson et al. 1994; Giuliani et al. 1995; Sasson et al. 1994; Heulitt et al. 2000, 2003; Sanders et al. 2001). However, current ventilators are microprocessor controlled, replacing mechanical responses to patient triggering seen in older generation ventilators. The result of the microprocessor controller is a faster response time with decreased trigger delay. This improvement may negate the advantages in adult patients with larger endotracheal tubes and mature respiratory muscles. This does not appear to be true in neonatal and pediatric patients. As can be seen in Fig. 15.2 (Sanders et al. 2001), flow triggering results in a faster response time and decreased effort necessary to trigger in a pediatric-sized animal model during pressure support ventilation. These differences are important because during triggering, the initial phase of patient effort reflects essentially patient work until the inspiratory valve opens completely and delivers gas to the proximal airway. This is illustrated in Fig. 15.3, where a tracing of pressure, flow, and

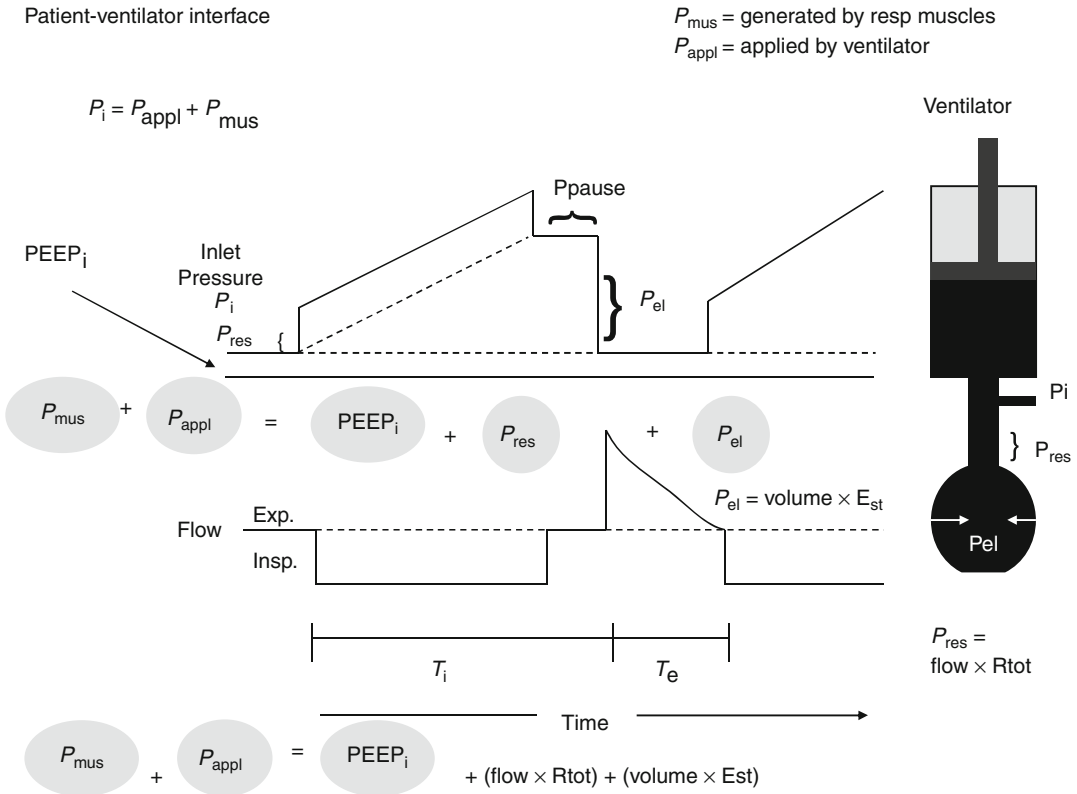


Fig. 15.1 The model on the right is of the respiratory system with the resistive elements represented by the straight tube and the elastic elements represented by the balloon connected to a ventilator represented as a piston. During inflation with a constant flow demonstrated in the lower waveform, there is a stepwise increase in the inlet pressure (P_i) that equals the loss of pressure across the resistive elements (P_{res}). Thereafter, P_i increases linearly and reflects

the mechanical properties of the elastic elements (P_{el}). P_i is the sum of P_{res} and P_{el} . P_{res} is the product of the total resistive components and flow. P_{el} is the product of the volume delivered and elastance of the respiratory system. At the end of inspiration, when flow has ceased which reflects the pressure at P_{pause} (insp. pause), P_i decreases by an amount equal to P_{res} , P_i equals P_{el} during Insp (Modified from figure used with permission from Hubmayer et al. (1990))

volume is recorded at an animal's airway during pressure support. In this example, there is a waveform illustrating the opening and closing of the inspiratory valve with a tracing of the animal's muscular response, illustrated by an EMG tracing of the diaphragm. In a study of pediatric-sized lambs, WOB during flow triggering was reduced by 47 % during pressure support and 19 % in CPAP (Carmack et al. 1995). However, there have been no controlled studies in pediatric and neonatal patients to determine if these differences affect outcome measures such as length of ventilation.

It is important to note that despite the differences illustrated in the type of triggering, there are also differences related to the design characteristics

of the ventilator. These differences relate to ventilator control algorithms that can affect trigger delay. Trigger delay is the time from the beginning of inspiratory muscle activity and the beginning of mechanical inflation (increase in pressure at the proximal airway). Increased trigger delay has been associated with the design characteristics of the pneumatics and electronics of ventilator system and correlated with respiratory drive (Leung et al. 1997) more time to trigger with less drive. This is especially important in small preterm infants, who have intrinsically short inspiratory times. For instance, if the inspiratory time is 0.2 s and the trigger delay is 100 ms, the patient will be halfway through the inspiratory phase before mechanical assistance is appreciated.

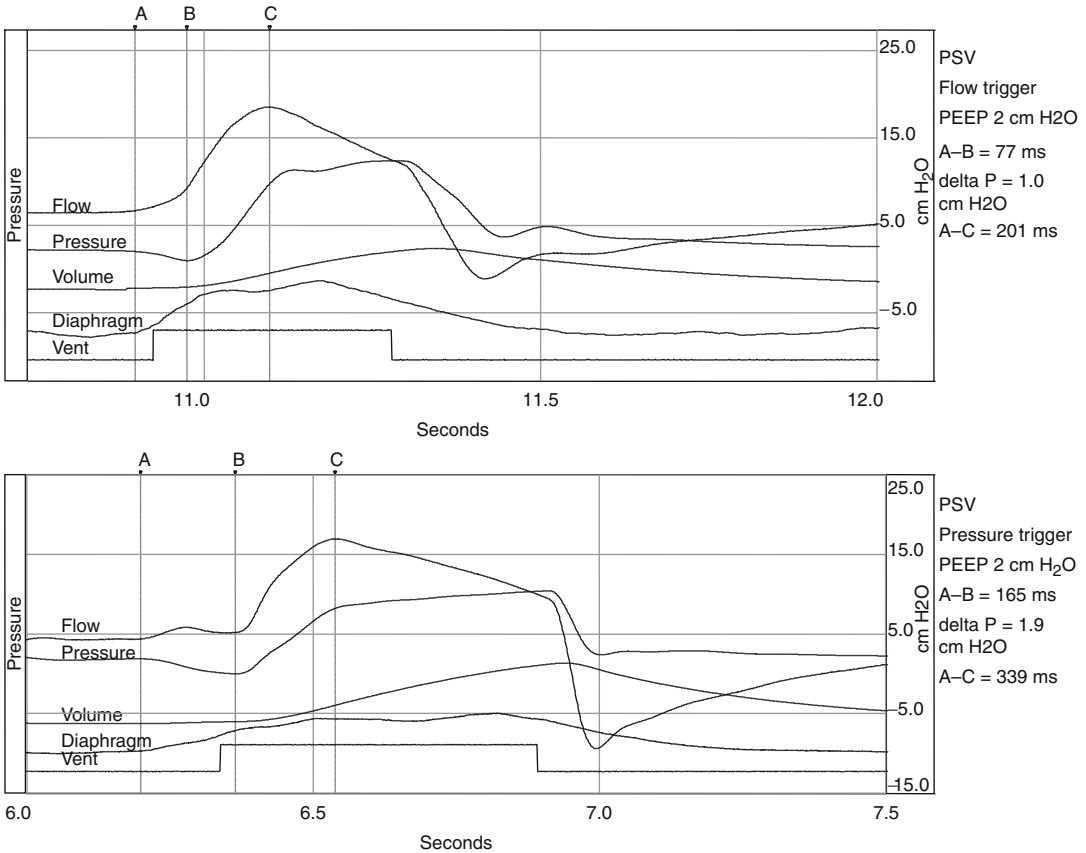


Fig. 15.2 Represents two waveforms. The *upper* waveform represents a single breath of a spontaneously breathing animal on pressure support being flow triggered. The *bottom* waveform represents a pressure-triggered breath. The negative pressure generated by the animal during

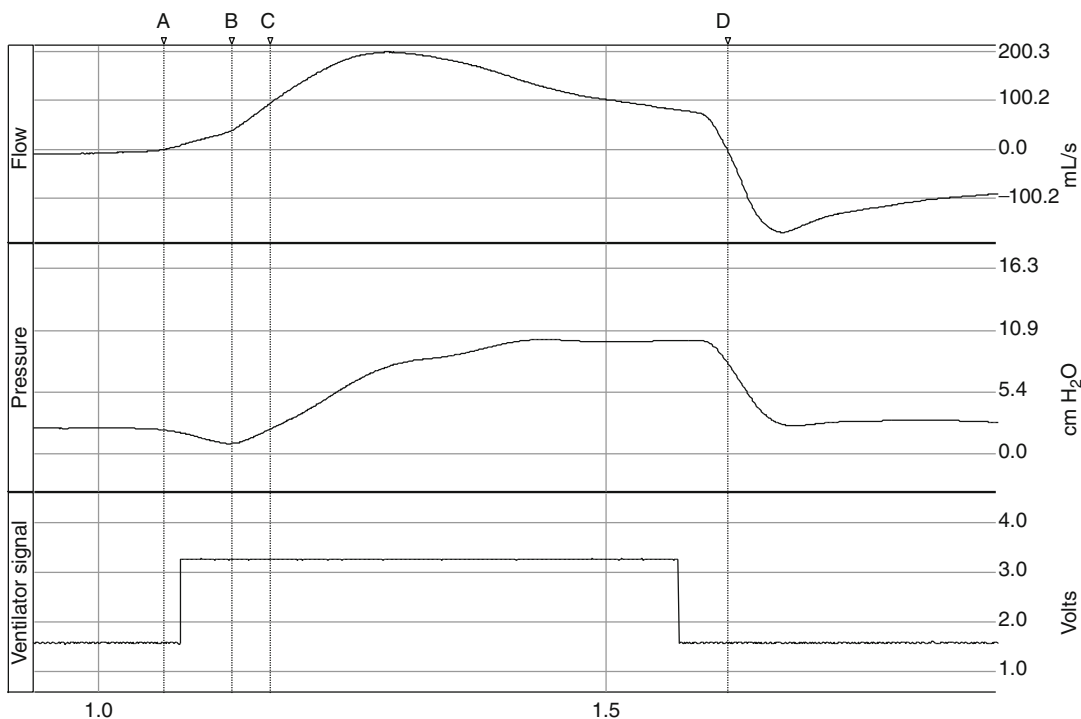
triggering of the pressure-triggered breath is almost double of the pressure necessary to trigger the flow-triggered breath. Also there is evidence of increased trigger delay in the pressure-triggered breath. A initiation of breath, B most negative pressure, C peak flow

In a study between two microprocessor-controlled neonatal ventilators, it was found that there was a significant difference in trigger delay and work of breathing between these two ventilators (Heulitt et al. 2000) illustrating the role of ventilator design on both work of breathing and triggering. Once triggering occurs, there is pressurization of ventilator circuit and subsequently the patient.

15.2.3 Factors Affecting Pressure Delivery

Control variables include pressure, flow, and volume. Once the trigger variable is met and the

inspiratory valve opens fully, there is pressurization of the ventilator circuit by the delivery of fresh gas flow. This pressurization of the system is illustrated in Fig. 15.4. The phase of this pressurization can be subdivided into the inspiratory positive pressure area or area 2 on Fig. 15.4 (Chatmongkolchart et al. 2001), which follows area 1, and is the amount of effort expended to activate the mechanical breath. Area 2 is defined by the start of the inspiratory pressure curve with the return of pressure to baseline and ending at the onset of expiration. Area 2 represents the ability of the ventilator to pressurize the system or the actual area of pressure versus time applied during inspiration. The variables that control the delivered pressure depend upon the



A – initiation of breath (zero flow)
 B – beginning of ventilator pressurization
 C – return to baseline pressure
 D – end inspiration

Seconds

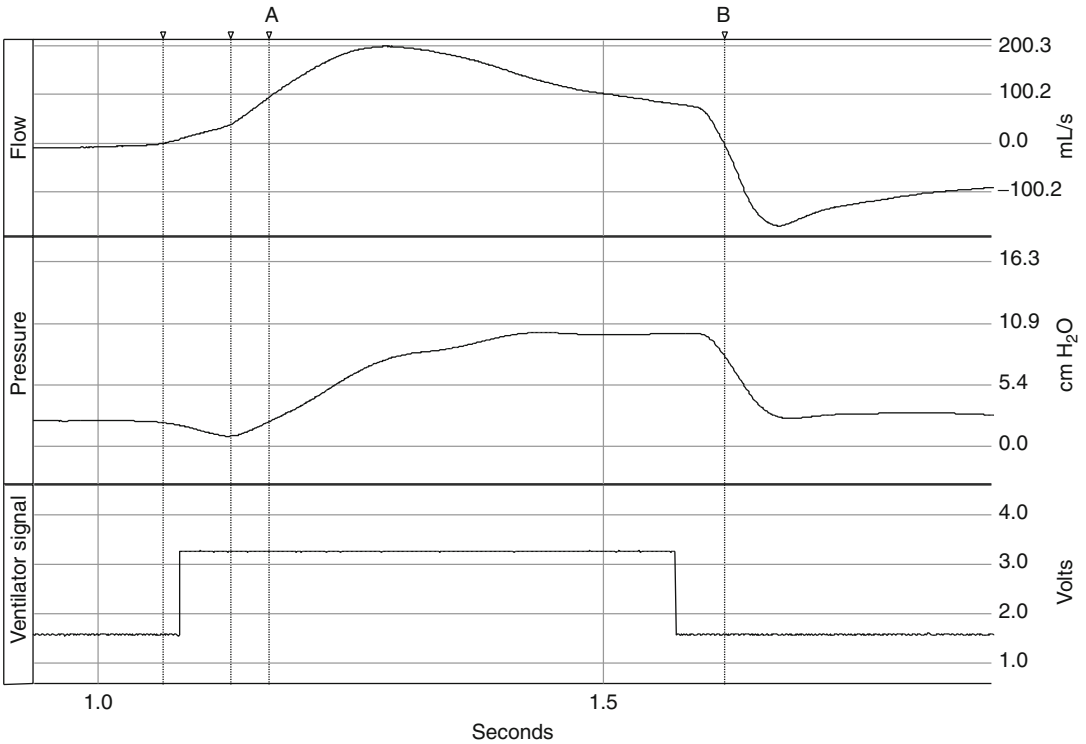
A – B = Trigger delay and PTP area A
 B – C = Response Time and PTP area B
 A – C = PTP area 1 (area A and area B)
 C – D = PTP area 2 (PTP of pressure curve during inspiration) tt

Fig. 15.3 Waveforms of flow, pressure, ventilator signal, and diaphragmatic (edi) signal are displayed. A is the beginning of the edi signal, B the initiation of the breath where

flow is a zero, C is the peak inspiratory flow, D the end of the edi signal. From point B to C, the line represents the slope of the inspiratory flow

mode of ventilation and the controller utilized in that mode. For example, in a mode with a preset tidal volume (e.g., volume assist-control), upon triggering the ventilator operates under a preset flow-time profile for the delivery of the tidal volume, and the ventilator determines the mechanical inflation time. In contrast, in a mode where there is a preset pressure (e.g., pressure support ventilation), the inflation time is influenced by both the patient and the ventilator. MacIntyre et al. (1990) demonstrated that if a rise in flow is not commensurate with the patient's demand during pressure support ventilation, there may be a too rapid rise in flow, or flow may be inadequate to meet the patient's

effort. In either case patient-ventilator asynchrony can result. Current ventilators also have dual control capability. Some modes (e.g., PAV, PRVC, VS) offer a theoretical compensation for these limitations. Breaths are regulated by one variable to meet a target variable. For example, in PRVC, the clinician sets a target volume and then regulates the delivered pressure between each breath to reach that volume target. In contrast, in PAV the ventilator delivers pressure that is proportional and set by the clinician to instantaneous flow and volume and thus the patient's own P_{mus} . Thus, depending upon the mode, it may or may not reflect corresponding changes in patient's effort.



A—Start of inspiratory pressure curve with return to baseline pressure
 B—Onset of expiration (flow crosses back across zero flow line)
 A–B = Area 2 (Area of the pressure curve during inspiration)

Fig. 15.4 The pressurization of the respiratory system is illustrated in the figure. The phase of this pressurization can be subdivided into the inspiratory positive pressure area or area 2 in the figure (Chatmongkolchart et al. 2001), which follows area 1, and is the amount of effort expended to activate the mechanical breath. Area 2 is

defined by the start of the inspiratory pressure curve with the return of pressure to baseline and ending at the onset of expiration. Area 2 represents the ability of the ventilator to pressurize the system or the actual area of pressure versus time applied during inspiration

15.2.4 Cycle Off Variable

The cycle off variable is the variable that controls the end of inspiration. This can be a clinician-controlled variable. As can be seen in Fig. 15.5, the timing of this trigger signal may not correspond to the end of neural inspiration and the peak of diaphragmatic activity or contraction of inspiratory muscles after the close of the inspiratory valve. Thus, if flow stops either before or after the patient's own inspiratory flow, expiratory flow occurs before the end of inspiratory effort. In this situation, P_{mus} continues to increase even though inspiratory flow is zero (inspiratory valve closed) or is reversed, and the muscle tension

is applied to the elastic recoil of the respiratory system rather than obtaining further inspiratory flow. Thus, at the end of mechanical inspiration, P_{mus} continues to increase the muscle tension applied to overcome elastic recoil of the respiratory system causes a short mechanical inflation and low elastic recoil at end-inspiration and can promote re-triggering or ineffective triggering. The effects of asynchrony depend on the type of asynchrony present (Georgopoulos and Roussos 1996) and will be discussed further below. In the newborn, use of flow cycling is important in achieving expiratory synchrony because of the rapidity with which the respiratory time constant can change.

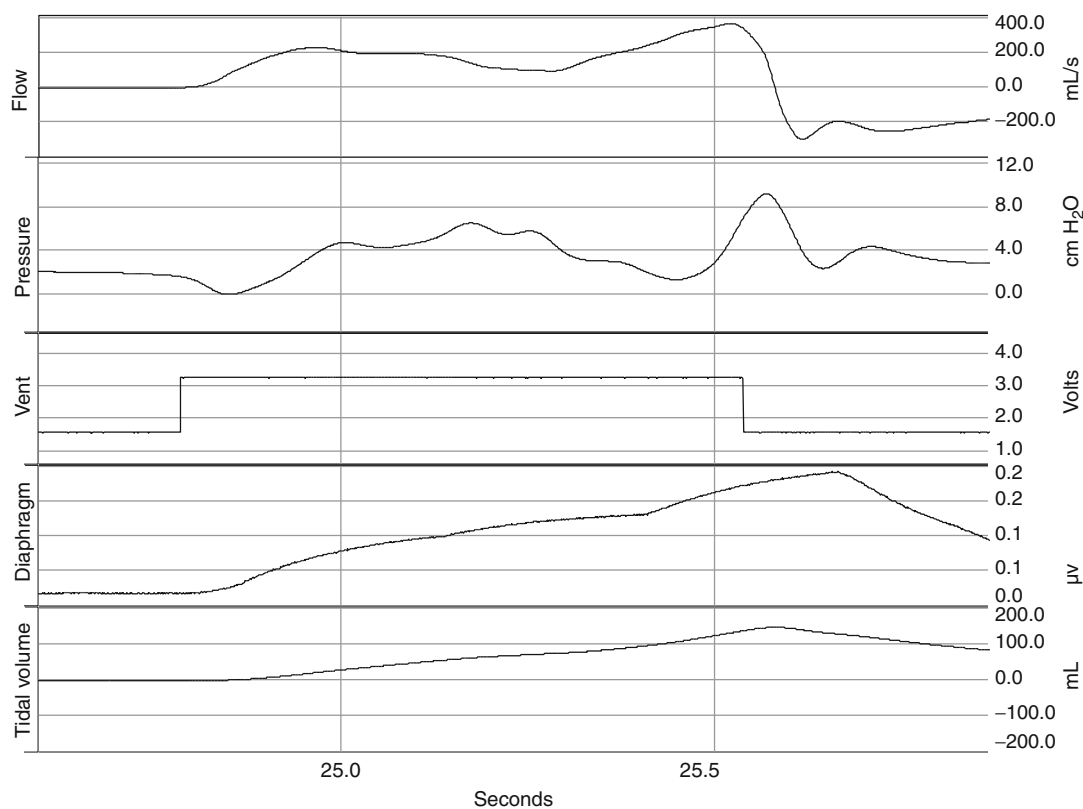


Fig. 15.5 Signals for flow, pressure, ventilator trigger, diaphragm EMG, and delivered tidal volume are displayed. The timing of this trigger signal may not correspond to the end of neural inspiration and the peak of diaphragmatic activity or contraction of inspiratory muscles after the close of the inspiratory valve. Thus, if flow stops either before or after the patient's own inspiratory flow, expiratory flow occurs before the end of inspiratory effort. In this situation, P_{mus} continues to increase even

though inspiratory flow is zero (inspiratory valve closed) or is reversed, and the muscle tension is applied to the elastic recoil of the respiratory system rather than obtaining further inspiratory flow. Thus, at the end of mechanical inspiration, P_{mus} continues to increase the muscle tension applied to overcome elastic recoil of the respiratory system which causes a short mechanical inflation and low elastic recoil at end-inspiration and can promote re-triggering or ineffective triggering

15.2.5 Patient-Related Factors

15.2.5.1 Mechanics of the Respiratory System and Characteristics of P_{mus} Waveform

Factors that affect flow because of the mechanical properties of the respiratory system and tubing can affect the pressure delivered by the ventilator (P_{aw}) independent of P_{mus} and may lead to asynchrony. This is usually seen when there is dynamic hyperinflation, where ineffective triggering, increased

trigger delay, or prolonged inflation are common.

However, the pattern of the P_{mus} waveform can affect P_{aw} in several ways, depending upon factors related to both the patient and the ventilator. If the patient has decreased drive, P_{mus} increases slowly, and the time between the onset of the patient's inspiratory effort and ventilator triggering increases, causing trigger delay with subsequent asynchrony. In contrast if the patient's inspiratory effort is vigorous and longer than mechanical inflation time, double triggering can occur.

15.2.5.1.1 Response of the Patient Effort to the Ventilator-Delivered Breath

Normal reflex responses to changes in chemical, mechanical, or receptor stimulation may cause physiologic changes that may be difficult to interpret by the clinician. For example, it is important to understand the role that mechanical feedback plays in the patient's response to a mechanically delivered breath. The mechanical feedback is related to the delivered lung volume (length of muscular contraction) and flow (velocity of the contraction) delivered. Thus, when lung volume and flow are greater, P_{mus} will be less. The exact role of mechanical feedback is not well understood and may play only a small role in patient-ventilator interactions, but in a situation of high ventilator demands with hypercapnic hyperventilation, P_{mus} may underestimate neural output to respiratory muscles and can be reduced by up to 15 % (Georgopoulos and Roussos 1996).

Another feedback mechanism involves the response of the respiratory system to PaO_2 , PaCO_2 , and pH or chemical feedback. In normal subjects in both wakefulness and sleep, chemical feedback determines respiratory motor output. In mechanical ventilation, it is theorized that neuromuscular output is tightly linked to carbon dioxide tension and not to load reduction on the respiratory system (Georgopoulos 1997). Thus, during mechanical ventilation, chemical feedback remains an important determinant of P_{mus} . However, these effects may differ substantially between wakefulness and sleep or sedation during mechanical ventilation.

During mechanical ventilation in a subject who is conscious, the effects of PaCO_2 cause an increased P_{mus} (respiratory effort) with no change in respiratory rate. However, respiratory rate increases if PaCO_2 increases considerably. In contrast, when the drive to breathe from wakefulness is reduced during sleep or sedation, the dependence of the respiratory rhythm upon PaCO_2 is increased (Skatrud and Berssenbrugge 1983; Younes 1989). Thus, any increase in V_T may induce periodic breathing and apnea. In patients with lung diseases such as pneumonia or ARDS, other inputs to the respiratory controller may prevent chemical feedback from diminishing the

tendency to increase neural inspiratory time and decrease neural expiratory time to a greater extent, resulting in a higher breathing frequency.

In addition to mechanical and chemical reflexes, other reflexes related to lung volume or flow changes – and mediated by receptors located in the respiratory tract – the lung and chest wall are important in controlling breathing (Shannon 1989; Younes 1981). These changes in volume and flow may elicit a P_{mus} response caused by other reflexes such as the Hering-Breuer reflex. The ultimate response is dependent upon the interplay of the magnitude and type of lung volume change, the level of consciousness, and the relative strength of the reflexes involved. In the premature infant, the chest wall is often more compliant than the lung, contributing to an increased work of breathing. An example of this interplay resulting in a misinterpretation by the clinician is demonstrated in a patient with decreasing levels of pressure support with the concomitant reduction in V_T and inspiratory flow. These changes cause a reflex feedback to increase neural inspiratory time and decrease neural expiratory time to a greater extent, resulting in an increase in breathing frequency. The resultant increase in respiratory rate may be interpreted by the clinician as intolerance by the patient to the attempt to wean ventilator support and thus delay further weaning by the clinician.

Finally, behavioral feedback is affected by changes in sedation, the sleep-wake state, and other aspects of the patient's environment and may play a role in the patient's response to ventilatory changes made by the clinician. For example, in an awake patient with increased airway resistance, ventilatory changes to compensate for hyperinflation may reduce inspiratory flow to values less than the spontaneous level causing perceived patient discomfort resulting in dyspnea with rapid shallow breathing and resultant patient-ventilatory asynchrony.

In conclusion, the interactions between the patient and the ventilator during assisted mechanical ventilation are complex. It may be difficult for the clinician to balance the clinician-controlled ventilator and the patient's own muscular or reflex response because of the

difficulty in interpreting ventilator changes and the patient’s physiologic response. The resultant patient’s response may either be a normal physiologic reflex or indicative of patient-ventilator asynchrony requiring further changes. Proper interpretation of patient-ventilator asynchrony requires accurate identification.

15.3 Patient-Ventilator Asynchrony

Patient-ventilator asynchrony is the failure of two controllers to act in harmony. The patient’s work of breathing and effort are affected by the ventilator’s ability to meet the patient’s peak inspiratory demand (Marini et al. 1985, 1986). The factors that affect patient-ventilator asynchrony are listed in Table 15.1 and can be subdivided into equipment factors, patient factors, and decision-making (clinician) factors. The evaluation of patient-ventilator asynchrony can also be subdivided into four phases. These phases consist of triggering, flow delivery, breath termination, and the effects of PEEP_i. For each phase, waveforms will be reviewed to demonstrate how the clinician can detect patient-ventilator asynchrony.

Table 15.1 Factors that affect patient-ventilator asynchrony

Patient factors	Hering-Breuer reflexes
	Respiratory muscle Weakness
	Respiratory system mechanics
	Pathology
	Leaks
Ventilator factors	Ventilator algorithms and control
	Trigger signal
	Cycling off
	Rate and character of inspiratory flow
	Intrinsic PEEP
	Leaks
Decision-making factors	Mode
	Level of support
	Level of sedation
	Nutritional support
	Other treatments

Asynchrony results in ineffective gas exchange and has been associated with gas trapping, thoracic air leaks, increased work of breathing, inconsistent tidal volume delivery, and even intraventricular hemorrhage in the preterm infant.

15.3.1 Trigger Asynchrony

Trigger asynchrony is defined as the presence of muscular effort without effective ventilator triggering. The incidence and occurrence of patient-ventilator asynchrony is not well studied in pediatric patients. Clinical studies in adults have demonstrated trigger asynchrony in all common ventilator modes. In studies by Jubran et al. (1995) and Parthasarathy et al. (1988), cycle dysynchrony during the PS mode occurs because of activation of abdominal musculature during the inspiratory phase, increasing patient effort and the number of failed trigger efforts.

In a recent study by Heulitt et al. (2009) of mechanically ventilated pediatric-sized animals receiving PSV, it was found that trigger asynchrony in healthy animals was evident in 13 % of breaths. After creating lung injury by saline lavage followed by lung recruitment with pulmonary compliance recovered to 60–70 % of baseline, evidence of trigger asynchrony increased to 60–70 %. Also there was evidence of increased trigger delay and increased work of breathing measured as pressure time product (PTP) in the pneumatically triggered breaths as compared to neurally triggered breaths. The most common form of trigger asynchrony is trigger delay. Trigger delay is important in infants and children because of their increased respiratory rate. For example if an infant is breathing 40 times per minute, their respiratory cycle is 1500 ms’s. If there is a trigger delay of 200 ms then this represents 13 % of their respiratory cycle where they are exerting an effort without a response.

The reduction in trigger delay is important when it is considered in regard to timing of actual triggering. These results demonstrate an advantage in neurally triggered breaths. In both healthy and recruited lungs, we found it took less time (ms) from the initiation of the breath to the beginning of the ventilator trigger and that the percent

of PIF at the beginning of the ventilator signal was less for neurally triggered breaths. In the recruited animals, this could also be explained by a higher respiratory drive exemplified by a difference in P0.1. These findings are consistent with a faster response to effort.

The actual differences between trigger delay between the healthy and recruited animals are interesting. The triggered delay in the recruited animals is less than in the healthy animals in neurally triggered NAVA breaths. Since P0.1 and delta time from initiation of breath to opening of the ventilator valve are less in the neurally triggered breaths, this may represent a difference in the flow control algorithm allowing for a more rapid response to the animals' attempt to receive flow from the ventilator system. However, the peak inspiratory flow is less in the neurally triggered breaths which is consistent with the finding of a higher rate of flow asynchrony in these breaths.

Trigger delay is a delay in the time from the beginning of inspiratory muscle activity to the beginning of mechanical inflation. Causes of trigger delay are listed in Table 15.2. Trigger delay and ineffective effort can be easily detected by recording esophageal pressure or monitoring diaphragmatic activity with its EMG signal. Inserting an esophageal catheter is, however, a relatively invasive procedure, but there are commercially available catheters that combine EMG sensors with a nasogastric tube to justify its placement. Unfortunately, only one ventilator manufacturer has the ability to monitor the EMG signal. The EMG catheter may be superior to an

esophageal balloon because it more closely reflects neural events (Parthasarathy et al. 2000; Sinderby et al. 1997). An alternative to an invasive catheter may be found by inspecting the flow waveform. Identifying the abrupt decrease in expiratory flow from the flow trajectory established earlier indicates either the beginning of inspiratory muscle contraction or relaxation of expiratory muscles during active expiration (Fig. 15.5). In either case, the point of expiratory flow deviation signifies the beginning of the triggering phase. This can clearly be seen in Fig. 15.5, where the ventilator trigger signal and diaphragmatic EMG are included (these signals enhance the flow signal but are not required). The time lag between this point and the point at which P_{aw} starts to increase is the trigger delay. If there is no mechanical breath following an abrupt fall in expiratory flow, this can be classified as an ineffective triggering. However, the clinician must not confuse changes in the flow signal caused by cardiac oscillations with ineffective efforts.

It is important to note that trigger delay is not always caused by poor inspiratory effort. In adult patients, it has been found that effort is more than a third greater when the threshold for triggering the ventilator is not reached than when it is. Breaths that do not trigger the ventilator have higher V_T and shorter expiratory time (Leung et al. 1997).

Trigger asynchrony can cause breaths to be stacked. This is defined by when the delta time between the ventilator's trigger is one half of the mean inspiratory time of the patient. These breaths are classified as stacked breaths. Stacked breaths occur with or without expiratory flow between triggers. Figure 15.6 illustrates stacked breaths. Auto-triggering, which refers to the phenomenon of the ventilator being triggered in the absence of patient effort, may also occur. This phenomenon may be caused by improper setting of the trigger threshold or P_{aw} distortions caused by circuit leak, presence of water in the ventilator circuit, or patient cardiac oscillations. Auto-triggering occurs frequently in neonatal patients because uncuffed endotracheal tubes are used. In small premature infants, clinicians often set a low trigger threshold to avoid ineffective triggering, and thus even small leaks will result in auto-triggering. It may be difficult to distinguish auto-triggering from rapid

Table 15.2 Trigger delay

Ventilator characteristics and settings	Type and setting of trigger
	Site of signal recording
	Valves
	Level of pressure assistance
Patient characteristics	Ventilator modes
	Dynamic hyperinflation
	Respiratory drive during trigger phase
	Upper airway resistance (during NIV)
Circuit characteristics and interfaces	Additional resistance (ET, ventilator circuit, airway sensor, HME)

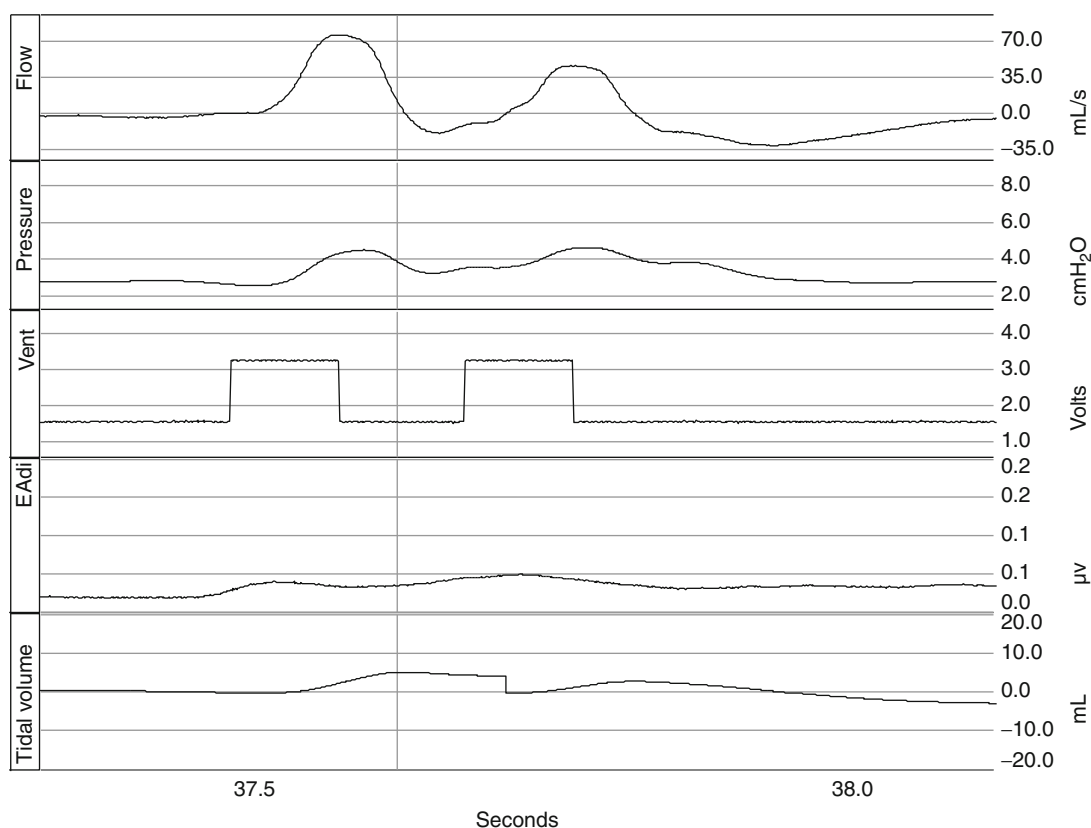


Fig. 15.6 Signals for flow, pressure, ventilator trigger, diaphragm EMG, and delivered tidal volume are displayed. This figure illustrates auto-triggering with evidence of ventilator response without evidence of patient effort in a spontaneous breathing, patient-triggered mode.

Auto-triggering can also be detected by inspection of the pressure and flow waveforms by identifying the absence of the initial pressure drop below end-expiratory pressure which would be required in patient-triggered breath

breathing in these patients. Auto-triggering should be suspected when each breath looks identical and occurs at regular intervals. Rapid breathing will show some variability in rate and the appearance of the waveforms. Figure 15.7 illustrates auto-triggering with evidence of ventilator response without evidence of patient effort in a spontaneous breathing, patient-triggered mode. Auto-triggering can also be detected by inspection of the pressure and flow waveforms by identifying the absence of the initial pressure drop below end-expiratory pressure which would be required in patient-triggered breath.

Another issue that can influence triggering of the ventilator leading to ventilator asynchrony is the presence of increased airway resistance leading to the presence of inadvertent positive end-expiratory pressure, $PEEP_i$. Mechanically

ventilated patients with obstructive lung disease who develop $PEEP_i$ have to generate a negative intrapleural pressure to match the value of $PEEP_i$ in addition to the ventilator sensitivity threshold level before triggering occurs and a ventilator breath is initiated. When inspiratory effort by the patient is less than the threshold value, the ventilator will not deliver a breath, causing effort without response from the ventilator. This is illustrated in Fig. 15.8, where there is clear evidence of muscular activity but no evidence of ventilator response. Therefore, dynamic hyperinflation ($PEEP_i$) leads to frequent non-triggering of breaths in patients with obstructive lung disease. Such non-triggered breaths represent wasted effort on the part of the patient and lead to patient-ventilator asynchrony. In any spontaneous breathing mode, the ventilator must be set to

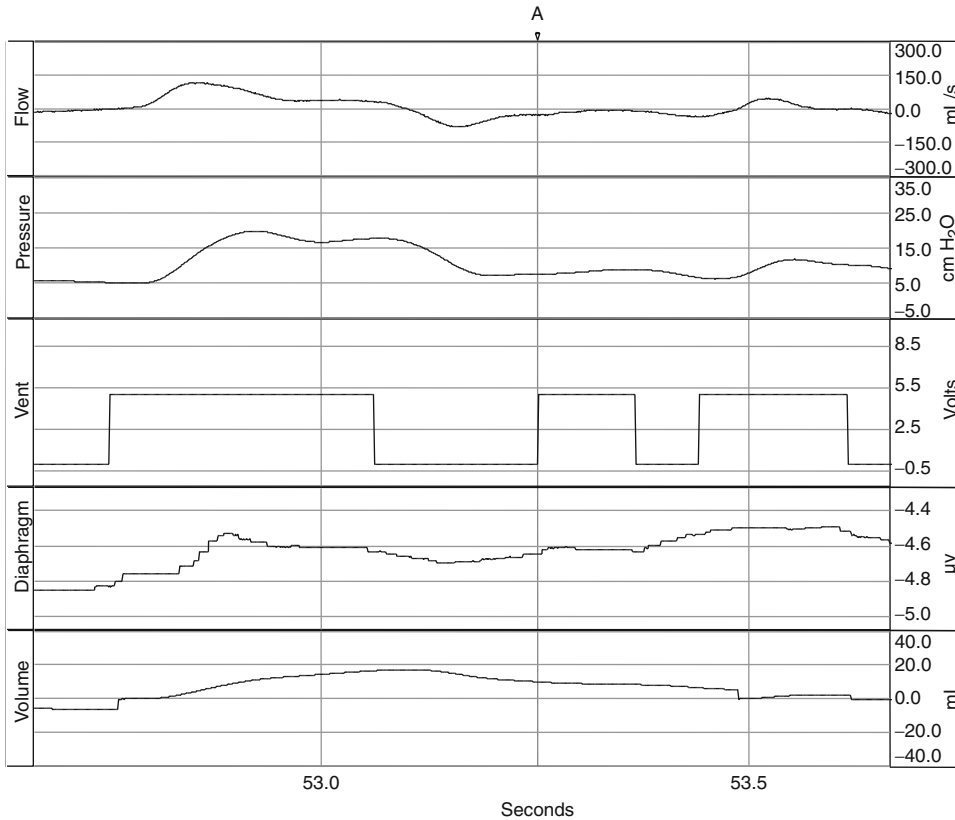


Fig. 15.7 Signals for flow, pressure, ventilator trigger, diaphragm EMG, and delivered tidal volume are displayed. There is clear evidence of muscular activity but no evidence of ventilator response. A indicates the point where flow crosses the zero flow line in a positive direc-

tion indicating effort to trigger. As indicated by A above, an effort was made to trigger the ventilator; however, there was no corresponding response. Mode is volume support ventilation

respond to the patient's breathing effort in order to provide adequate support. In addition, application of external PEEP could reduce the elastic threshold load and WOB, particularly in patients with flow limitations during tidal expiration.

15.3.2 Flow Asynchrony

Flow asynchrony occurs whenever the patient and the ventilator flows do not match. Flow from the ventilator can be a fixed or constant flow pattern (such as volume-controlled ventilation) or can be variable (PC, PS, or PRVC). In VC, flow is fixed

so that a set level of flow is delivered with each breath. Because WOB is the sum of the work performed by the ventilator and the work performed by the patient, reduction in ventilator support or work will reduce the level of support. During ventilation with variable flow, the peak flow depends upon on the set target pressure, the patient's effort, and the respiratory system compliance and resistance. During PC, the clinician can set the target pressure and the rate of flow acceleration or rise time. Ideally, in pressure ventilation, the rise in gas flow should match the patient's demand for flow. The control of flow acceleration varies according to the manufacturer of the ventilator,

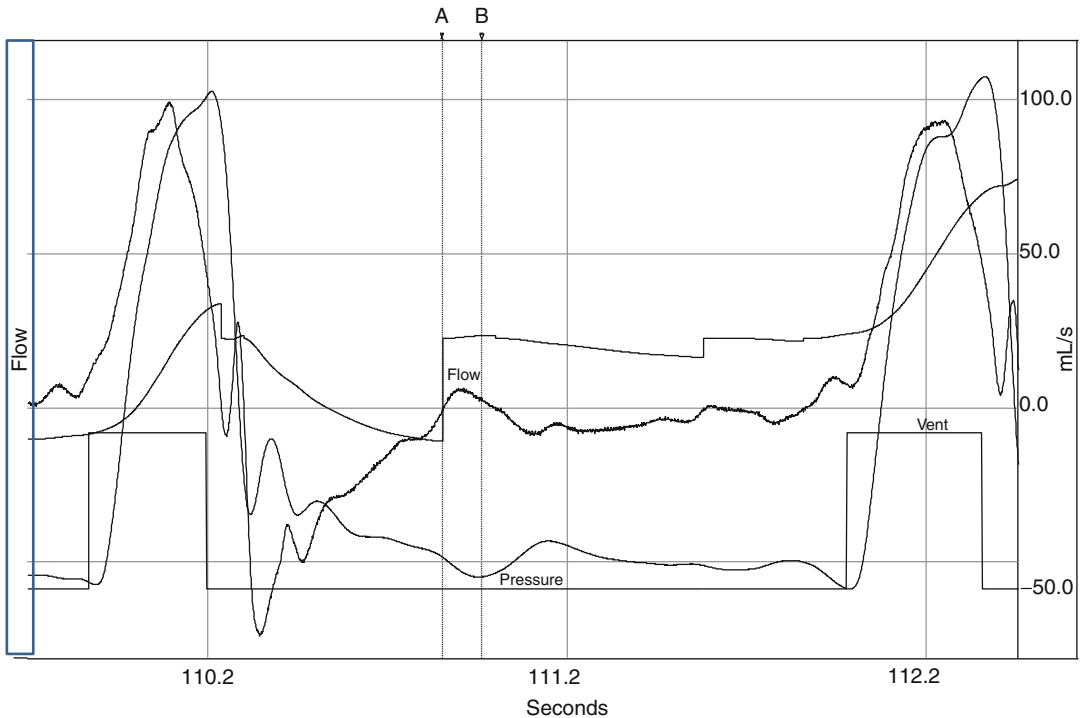


Fig. 15.8 On most pressure-volume loops, the pressure is plotted on the *x*-axis and volume and on the *y*-axis. Patient-triggered breaths will look different from time-triggered or machine-triggered breaths on the pressure-volume loops as the patient generates a negative pressure

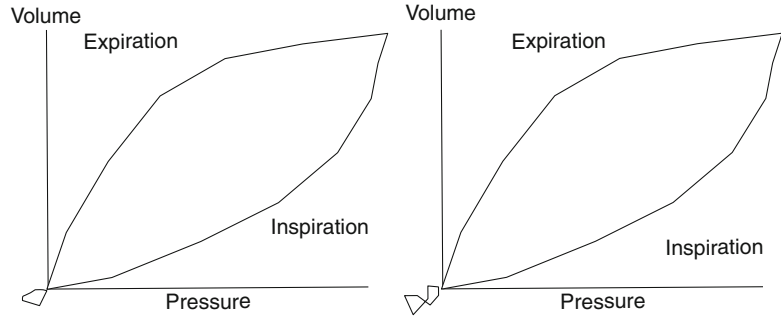
at the beginning of inspiration. A shows a patient-triggered breath and the resulting pressure-volume loop that traces the inspiration and exhalation. Pressure-volume loop B represents a single breath with excessive triggering effort reflected by the classic “Figure 8” pattern

but the principles remain the same. Changing the rise time can have a profound effect on the flow-time waveform (Mancebo et al. 1995). If the rise time is set to the fastest setting (rise time 0), a sharp increase in inspiratory flow is dictated by the interaction between P_{mus} , P_{aw} , and elastic recoil at end-expiration (Bonmarchand et al. 1996). It has been reported that a very high pressurization rate has been associated with presence of a pressure overshoot causing a sense of dyspnea in the patient. A slower rise time may limit the ability of the ventilator to meet the patient's demands. Studies of flow asynchrony during PC or PSV have implied that many patients require a rapid rise time to match increased ventilatory demand. MacIntyre et al. (1997) assessed whether adjustments in the initial flow or breath termination criteria affect patient-ventilator synchrony. The

ventilator pattern response to PSV in 33 adult patients was studied under conditions with two parameters: seven different levels of delivered initial PSV flow and during PSV termination at 50 and 25 % of peak flow. They found an optimal initial flow could be defined for a given PSV level, which resulted in the patient gaining a maximal pressure and volume from the ventilator. In addition, the initial PSV flows above and below this optimal flow were associated with faster breathing rates (or minute ventilation), shorter inspiratory times, smaller tidal volumes, and a tendency for airway pressure to meet the preset value. In pediatric patients who have smaller endotracheal tubes, increased flow may lead to increased turbulence and, possibly, increased asynchrony.

Figure 15.6 illustrates flow asynchrony, with the common finding seen as concavity in the

Fig. 15.9 Pressure volume curves in a spontaneous breathing subject. The portion of the curve extending beyond the origin of the figure represents the patient's work of breathing. The second figure demonstrates increased work of breathing because the area, thus effort is greater than the first figure with a "Fig. 15.8" configuration



pressure waveform illustrating inadequate flow to meet the patient's needs. Also this can be illustrated in a pressure-volume loop with evidence of the classic "Figure 8" due to increased triggering effort by the patient and turbulence (Fig. 15.9).

15.3.3 Termination Asynchrony

Termination asynchrony occurs when neural inspiratory time and ventilator inspiratory time do not coincide. The ability of the ventilator mode to terminate a breath when the patient desires a longer inspiratory time constitutes an important factor in reducing the incidence of dyssynchrony. For example, in pressure support inspiration is terminated by one of three mechanisms. The primary method is a decrease in flow. The second is a rise in pressure above the target setting. The third is inspiratory time exceeding a specific maximum duration. Termination asynchrony can be caused by delayed termination or premature termination. Termination asynchrony is defined as an increase in the expiratory portion of the airway pressure waveform (e.g., >2 cm H₂O). This occurs when the peak of muscle activity occurs before the inspiration valve is closed. This is illustrated when there is a peak in PIP beyond the close of the inspiratory valve but after the peak of respiratory muscle activity exemplified by the EMG of the diaphragm or Edi signal. The most common type of termination asynchrony is delayed termination. Generally, delayed termination results in dynamic hyperinflation, with

resultant trigger delay and increased missed trigger attempts. Premature termination can also have deleterious effects with resultant asynchrony. In a study by Tokioka et al. (2001), premature termination led to substantially reduced V_T , increased respiratory rate, decreased inspiratory time, and increased WOB. In addition, in a study by Yamada and Du (2000) that mathematically modeled the transition from inspiration to expiration and determined that the relationship of flow at the end of a patient's neural inspiratory time to peak inspiratory flow is related to two factors, the ratio of the respiratory time constant to the patient's neural inspiratory time and the ratio of the set PS level to the maximum inspiratory muscle pressure. Thus, with set inspiration termination criteria, a patient can end inspiration before or after the ventilator reaches it termination flow. This variability in inspiration termination criteria clearly increases the probability of patient-ventilator synchrony.

15.3.4 Expiratory Asynchrony

Expiratory asynchrony results from a shortened or prolonged expiratory time and the patient attempting effort during expiration when the ventilator is unresponsive. Shortened expiratory time creates the potential for hyperinflation secondary to air trapping with generation of PEEP_i. This can occur in ventilator systems with and without active expiratory systems. It is assumed that the incidence is decreased in an active expiratory system, where ventilator response to patient effort in expiration can occur.

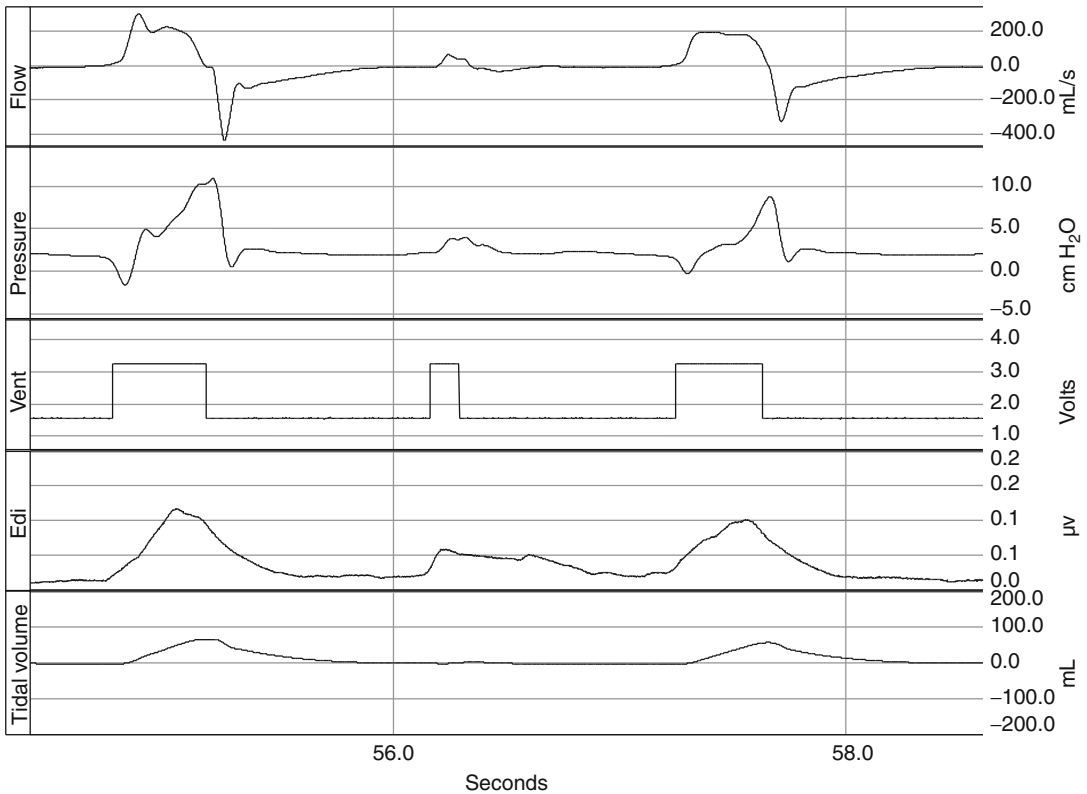


Fig. 15.10 This figure illustrates short cycle asynchrony. Short cycle is when inspiratory time is $< \frac{1}{2}$ the mean inspiratory time for the breathe studied

15.3.5 Short and Prolonged Cycled Asynchrony

Further asynchrony can be defined as short cycled or prolonged cycled. Short cycled is when inspiratory time is $< \frac{1}{2}$ the mean inspiratory time for breaths studied. This is illustrated in Fig. 15.10. Prolonged cycle is when the inspiratory time is > 2 times the mean inspiratory time for breaths studied (Fig. 15.11).

Future Perspectives

Current clinical trends require a better understanding of the interactions between the spontaneously breathing patient and the ventilator because of the recommendations for patients to be maintained at a higher level of wakefulness during mechanical ventilation. Research in the future needs to

define the advantages and disadvantages of this practice and further investigate the effects of sleep in these patients. Future advances in mechanical ventilation may require a closed-loop system that would allow the patient and ventilator to interact independently of the clinician to allow for better patient-ventilator synchrony.

Essentials to Remember

- Newton's equation of motion explains the interaction between the patient's generated pressure represented by P_{mus} and the ventilator's generated pressure P_{appl} and represents the pressures necessary to overcome the system.
- Factors affecting the response of the ventilator to the patient can be subdivided

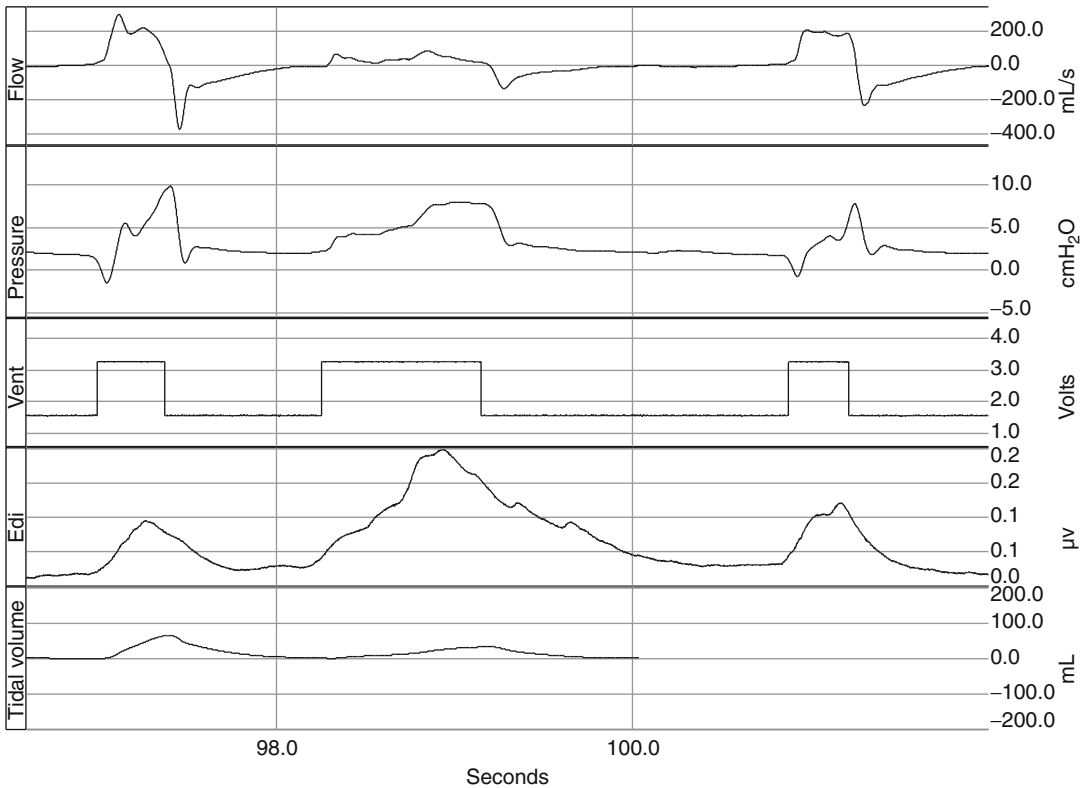


Fig. 15.11 This figure illustrates prolonged cycle asynchrony. Prolonged cycle asynchrony is when the inspiratory time is > 2 times the mean respiratory time for the breaths studied

into the ventilator factors affecting the initiation of the breath (trigger variable), how the breath is sustained (gas control variable), and how the breath is terminated (cycle off criterion).

- Patient-related factors include the mechanics of the patient's respiratory system and characteristics of the patient-generated muscular response or pressure generated by the patient's respiratory muscles or P_{mus} .
- Patient-ventilator asynchrony is the failure of two controllers to act in harmony.
- The factors that affect patient-ventilator asynchrony can be subdivided into equipment factors, patient factors, and decision-making factors.

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Basic and Practically Useful Respiratory Monitoring of a Mechanically Ventilated Patient in Resource-Limited Countries

Andrew C. Argent

Educational Aims

- Identify techniques and technologies that provide useful information for effective and safe ventilation, at costs that are reasonable within resource-limited environments.
- Focus on information that is relevant to the management of the ventilated patient.
- Consider cost-benefit aspects of various monitoring equipment.

16.1 Introduction

The development of intensive care has seen a proliferation of devices for patient monitoring. An underlying assumption has been that improved monitoring can only result in improved patient care. In fact increasing complexity of the intensive care environment, increased presentation of

data, and the presence of multiple alarm system may lead to deterioration in the quality of care as staff are overwhelmed by the complexity and volume of information (Frey and Argent 2004).

Over the years a wide variety of techniques have been developed for respiratory monitoring in intensive care including blood gas analysis; transcutaneous blood gas monitors; saturation monitors; end-tidal monitors; pressure, flow, and volume monitors with a variety of modes of data presentation; X-rays and computerized tomography; ultrasonography; electrical impedance tomography; and respiratory impedance plethysmography. Many of these techniques have developed in the context of research, and relatively few have been carefully assessed for their utility in optimization of clinical care. Even fewer techniques have been thoroughly assessed in children of all ages.

When monitoring respiratory function, the intensivist may have a range of concerns. As an example, the ideal blood gas in a particular patient will depend on a wide variety of clinical issues which have to be balanced by the clinician in order to set appropriate goals of ventilation. This may include respiratory concerns such as the ventilatory interventions required to achieve particular blood gas values; effects of ventilation on the cardiovascular system; other organ concerns such as intracranial pressure and brain perfusion; and the presence of infection.

Ideal monitors and monitoring systems would be noninvasive; simple to apply and use; consistently accurate in a wide range of clinical contexts; applicable to children of all ages and size;

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and relatively inexpensive. The ideal monitor would also provide information that is clinically relevant, or in other terms, appropriate utilization of the data provided by the monitor should result in improvement in patient outcomes.

16.2 Basic Monitoring

The starting point for all monitoring in the PICU should be careful observation of the patient, and a basic requirement for monitoring is a regular assessment of patient comfort. Recently Cretikos et al. (2008) have reviewed the clinical significance of the respiratory rate and reported that in adult medicine it is the vital sign least often recorded and most frequently completely omitted from hospital documentation. A raised respiratory rate is a strong and specific predictor of serious adverse events such as cardiac arrest and unplanned intensive care unit admission.

Unfortunately, there is limited data on the reliability of clinical signs. There may be significant interobserver differences in the assessment of clinical signs such as bronchial breathing (Morrow et al. 2010) and stridor (Kemper et al. 1992), but several studies have confirmed the reliability of scoring systems in conditions such as asthma (Liu et al. 2004). There is a need for studies of the relationship between clinical signs and objective measures of physiological function.

16.3 Monitoring of Blood Gases

16.3.1 Blood Gas Analysis

Blood gas analysis has been used as the gold standard for measurement of the effectiveness of ventilation. The particular problem related to blood gas analysis is that it is invasive (and potentially painful) and requires the sampling of blood, increasing the need for blood transfusion with associated potential complications. Intermittent blood gas sampling can be done via indwelling vascular lines (with associated complication rates), via phlebotomy, or via capillary blood collection. Intermittent arterial puncture is painful,

and the results obtained may be difficult to interpret if the patient was significantly disturbed during the collection of the specimen. Indwelling vascular lines are associated with complications that may be more frequent in particular groups of patients (HIV (Island et al. 2001; Roilides et al. 1991), diabetes (Worly et al. 2004), those with bleeding problems, etc.). Improvements in success in placement of arterial lines by the use of ultrasonography have recently been described in infants (Schwemmer et al. 2006).

A number of intravascular catheters are now available for continuous measurement of pO_2 , pCO_2 , and pH. Some of these can be used as arterial catheters (Rais-Bahrami et al. 2002a, b) (although the Neotrend/Paratrend is no longer produced), while more recent has been the development of intravascular venous saturation probes (Ranucci et al. 2008).

16.3.2 Saturation Monitoring

Monitoring of oxygenation was absolutely revolutionized by the introduction of saturation monitors.

The topic of oxygen monitoring, particularly in the context of the developing world, has recently been reviewed by Duke et al. (2009). A Cochrane review of adult postoperative saturation monitoring concluded that saturation monitoring was able to identify periods of hypoxemia, and the authors concluded that there was not sufficient evidence to show that it changed management (Pedersen et al. 2009). However, there are other studies showing that oxygen therapy linked with monitoring (using pulse oximetry) has been associated with significant decrease in mortality from pneumonia (Duke et al. 2008). Thus current expert opinion from anesthesiology and pediatrics (Duke et al. 2009) is that pulse oximeters should be made available throughout the developing world to improve the management of children with potential hypoxemia.

There are some constraints to saturation monitoring. As pointed out by Caples and Hubmayr (2003), given the shape of the oxyhemoglobin dissociation curve, within 4 % of an oxygen saturation

of 95 % would yield a wide pO_2 range of 60–160 mmHg. Thus pulse oximetry is not accurate for the detection of hyperoxia (particularly in preterm infants). It may also be difficult to use on patients with poor cardiac output, poor tissue perfusion, hypothermia, or restlessness. Pulse oximetry may also be inaccurate at low oxygen saturations and in the presence of abnormal hemoglobin (including carboxyhemoglobin).

Although pulse oximeters have a wide range of prices, it is possible to obtain reliable pulse oximeters for low prices, and many models are robust enough to be used under very arduous conditions.

16.3.3 Transcutaneous Monitoring of pCO_2 or pO_2

Transcutaneous monitoring has the advantage that it provides continuous data without blood sampling and without the placement of invasive catheters.

However, placement of these probes is relatively time-consuming and involves both placement and calibration. Probes' positions have to be changed every 4–6 h to prevent local skin damage, particularly in patients with sensitive skin or poor perfusion.

Use of transcutaneous monitoring has recently been reviewed by Tobias (2009). There is evidence to show that it is as reliable as end-tidal CO_2 monitoring (see below) in patients with normal lungs and better than $ETCO_2$ in patients with problems such as congenital heart disease, extrapulmonary shunts, and ventilation perfusion mismatch. In addition it may be used in a number of situations (e.g., high-frequency ventilation) where it is not possible to use end-tidal CO_2 monitoring. In neonates several studies have shown better correlation between arterial and transcutaneous pCO_2 (Geven et al. 1987; Hand et al. 1989) than between arterial and end-tidal pCO_2 .

The equipment is relatively expensive and is demanding on time for responsible staff. In addition there is a tendency for high and low pCO_2 levels to be exaggerated by the transcutaneous method (Hejlesen et al. 2009). However, these

costs must be weighed against the potential benefits of being able to monitor CO_2 levels continuously without invasive vascular lines, particularly in patients at high risk of adverse effects related to pCO_2 levels (e.g., head trauma with raised intracranial pressure or the premature infant with high risk of periventricular leukomalacia).

16.3.4 Tissue Monitoring

Devices which will provide an assessment of tissue oxygen saturation, using techniques such as near-infrared spectroscopy (Chakravarti et al. 2008), or tissue oxygen pressure (Rohlwick and Figaji 2010) are available, but would not usually be either available or appropriate in resource-limited situations.

16.3.5 End-Tidal Monitoring ($ETCO_2$)

Assessment of end-tidal pCO_2 ($ETCO_2$) can be done using a variety of methods including colorimetric capnography, sidestream and mainstream (Bhat and Abhishek 2008) capnography (with measurement done at the ventilator end of the endotracheal tube), and capnography on gas obtained from the distal end of the endotracheal tube (Kugelman et al. 2008). $ETCO_2$ is not a direct reflection of arterial pCO_2 , as it may be affected by many factors. However, there is a reasonable correlation between the pCO_2 in gas at the end of expiration and alveolar pCO_2 as long as there is an adequate “plateau phase” at the end of expiration.

Capnography has been shown to be useful for confirmation of endotracheal tube placement (DeBoer and Seaver 2004) in both neonates and children (Wyllie and Carlo 2006; Sullivan et al. 2005; Tingay et al. 2005; Erasmus 2004) with the proviso that problems may arise during cardiac arrest (in this situation no CO_2 is delivered to the lungs, and so capnography is inappropriate for monitoring of appropriate endotracheal placement). In addition colorimetric $ETCO_2$ detectors cannot detect hypocarbia or hypercarbia, bronchial intubation, or oropharyngeal intubations in spontaneously breathing patients (Bhende 2001).

Table 16.1 Monitoring of the ventilated patient

Mode	Process	Comment
<i>Blood gas related</i>		
Blood gas analysis	Requires collection of blood specimens, and is thus invasive, and may be associated with increased need for blood transfusion	Generally used commonly, but role may be decreasing with increasing availability of noninvasive monitors of pO ₂ and pCO ₂
Transcutaneous monitor	Provides constant data on pO ₂ and pCO ₂ without blood collection or vascular access	More expensive equipment and consumables and requires extra nursing attention to move probes and monitor sites
Saturation monitors	Provides continuous data on oxygen saturation. Simple to use and reliable technology. Not good for identification of high pO ₂	Increasingly recognized as essential equipment when treating any patient with potential hypoxemia
End-tidal CO ₂ monitors and capnography	Provides continuous data but may be technically challenging to get accurate data, particularly if large leaks around ETT	Recommended as essential equipment to confirm endotracheal intubation. Useful in monitoring of patients on conventional ventilators when other parameters are stable
Tissue oxygen monitors (including NIRS)	Have generally been used for monitoring of cardiac output rather than ventilation	Expensive equipment and consumables. Has not been widely used for monitoring of ventilation but possibly has important potential
<i>Respiratory mechanics measurement</i>		
Airway pressures	Part of basic ventilator monitoring. Particular important if on volume modes of ventilation	May be significant inaccuracies on some ventilators
Flow and tidal volume	Part of basic ventilator monitoring. Particular important if on pressure modes of ventilation. Tidal volume is the one parameter that has been shown to correspond with outcomes	Some ventilators are significantly inaccurate in measurement of tidal volumes. Relatively inexpensive monitors can be purchased to measure flow and tidal volume at the ETT
Pressure-volume curves	Available on many ventilators. Provide useful physiological data, but have not shown to improve patient outcomes	Not part of essential monitoring, although may help with
Electrical impedance tomography	Newly developing technology that may provide information on regional ventilation	Expensive, not generally available commercially, and complex to use

End-tidal monitoring of pCO₂ for ongoing ventilation is more complex with significant differences between measured arterial pCO₂ and ETCO₂ in several situations including trauma (Warner et al. 2009; Lee et al. 2009), congenital heart disease (Wilson et al. 2005), and significant lung disease. In addition ETCO₂ monitoring cannot be used in children on high-frequency ventilation. Close attention needs to be paid to the design of the device used to measure ETCO₂, as the devices may add significant dead space, particularly in small infants. Recently Kugelman et al. (2008) reported on the use of ETCO₂ monitoring from the distal end of a double-lumen endotracheal tube (such as would be used to administer agents such as surfactant to neonates) and showed that this may be substantially more accurate than the use of conventional side- or mainstream monitors.

Greer et al. (2003) have shown some data suggesting that it may be possible to use ETCO₂ to optimize tidal volume in small infants.

In addition to the end-tidal CO₂ level, it is possible to assess a number of variables (including dead space) from analysis of the expired CO₂ profile following administration of 100 % oxygen (Main and Stocks 2004; Main et al. 2004); this technique has not been used for general monitoring of ventilation (Table 16.1).

16.4 Respiratory Mechanics Measurement

Most ventilators provide data on the ventilator regarding airway pressures, and increasingly modern ventilators have displays of both flow and tidal volume. However, there is considerable data that

measurements may be significantly inaccurate. For monitoring purposes it is important to measure dependant variables. Thus during pressure control ventilation, it is most important to monitor flows and tidal volumes, while during volume control ventilation, it is important to monitor pressures.

16.4.1 Pressures

Measurement of airway pressure in a ventilator is fundamental to the management of ventilation (using both pressure and volume modes). Display of the pressure trace, as opposed to a digital display or an analog display, enables much clearer analysis of the pattern of ventilation that is actually being administered.

There is some data that airway pressures measured at the endotracheal tube are similar to those measured in the ventilator circuit (Cannon et al. 2000). However, Nasiroglu et al. (2006) compared the pressure measured in the ventilator circuit proximal to the endotracheal tube with the pressure in the trachea on a group of 30 children (aged 29 days to 5 years) and showed that there were significant differences. Peak inspiratory pressures measured in the ventilator circuit overestimated tracheal pressure during positive-pressure ventilation and underestimated tracheal pressures during spontaneous ventilation. Similar findings have been reported by other authors (Dela Cruz et al. 2005). Nikischin et al. (2007; Nikischin and Lange 2003) have examined the impact of leaks on the relationship between airway and tracheal pressures and have suggested methods for correction of data.

16.4.2 Flow and Volume

Airflow during ventilation can be measured using a range of pneumotachographs placed at a variety of places within the ventilation circuit. Care must be taken to ensure that the pneumotachographs are appropriately calibrated and that the geometry of the ventilatory circuits does not interfere with effective function (Kreit and Sciurba 1996). Respiratory impedance plethysmography can also be used to measure gas flows (Brooks et al. 1997) with the advantage that there is no insertion to

the respiratory circuit with additional resistance and dead space; however, respiratory impedance plethysmography does require calibration and may require more sophisticated resources.

There is substantial evidence that flows and tidal volumes measured at the endotracheal tube may be substantially different to those measured within ventilator circuits (Cannon et al. 2000; Al-Majed et al. 2004; Castle et al. 2002; Chow et al. 2002; Heulitt et al. 2005, 2009), and these differences may be affected by issues such as lung compliance and leaks around the endotracheal tube (Main et al. 2001; Herber-Jonat et al. 2008) or the use of heat moisture exchangers for humidification (Fujita et al. 2006).

This is of particular concern, as there is substantial evidence that tidal volumes are clearly related to inflammatory responses both systemically and within the lungs (Wolthuis et al. 2008) and many studies have highlighted the potential benefits of ventilation with lower tidal volumes in adults and children with ARDS and other lung conditions (Wolthuis et al. 2008; Amato et al. 1995, 1998; The Acute Respiratory Distress Syndrome Network 2000; Meade et al. 2008; Schultz 2008; Choi et al. 2006; Ferguson et al. 2005; Rimensberger et al. 1999; Brochard et al. 1998). And ventilation at lower tidal volumes has been associated with improved outcomes in pediatric patients with lung disease (Khemani et al. 2009; Randolph 2009; Hanson and Flori 2006; Mehta and Arnold 2004; Albuali et al. 2007).

Ideally flow and volume data should be graphically displayed (in conjunction with pressure data), as this enables optimization of inspiratory and expiratory times. Utilization of this data can prevent overdistension of the lung from “stacking” (Pohlman et al. 2008).

Particular attention needs to be paid to leaks around endotracheal tubes, which are almost the norm in smaller children where uncuffed endotracheal tubes have been used routinely for many years. With modern cuffed endotracheal tubes, it may be possible (and appropriate) to use cuffed tubes on younger infants, particularly those who are unstable at the time of intubation (Newth et al. 2004). Elimination of the leak makes it substantially easier to evaluate respiratory function in ventilated children.

16.4.3 Pressure-Volume Curves

A wide variety of curves and graphics can be generated using the interactions of pressure, flow, volume, and time. However, although they may provide promising and interesting data regarding lung and respiratory physiology, there is not data showing that their use changes patient outcomes (Terragni et al. 2003).

Much physiological data has been derived from static compliance curves, and much of the theory on optimal ventilation has derived from study of static compliance curves. However, as shown by Adams et al. (2001), the dynamic compliance curves that are displayed on many ventilators are very different to static curves and should not be used to define ventilatory strategies. In particular inflection points on compliance curves are often difficult to identify and may not be present on tidal pressure-volume curves (Albaiceta et al. 2008).

16.5 New Technology

Electrical impedance tomography (Frerichs et al. 2001; Heinrich et al. 2006; Wolf et al. 2007) has been used in a variety of settings to assess regional ventilation of the lung. It is however technically challenging and remains essentially a research tool in sophisticated settings, although more commercial systems may soon be available.

Conclusions

Clinical assessment of patients and their interface with ventilators remains a fundamental requirement for safe ventilation. However, clinical assessment does require the development of acute clinical skills, and this is difficult in the absence of additional monitoring and in the context of limited resources and substantial caseload.

Although a wide variety of techniques are available for the monitoring of ventilation in children, the only proven techniques are arterial blood gas analysis; capnography for rapid

identification of endotracheal tube placement; pulse oximetry for identification of poor oxygenation (not reliable for identification of hyperoxia); and measurement of pressure, flows, and tidal volume at the ETT.

Points to Remember

- Basic clinical monitoring is essential, with a particular emphasis on ensuring patient comfort.
- Blood gas analysis is the baseline for assessment of ventilation. It is however invasive and may have complications. Noninvasive monitoring of oxygenation and pCO₂ will be used increasingly.
- Oxygen saturation monitoring is essential in any child who may be hypoxemic, and equipment is relatively cheap and reliable.
- Monitoring of end-tidal pCO₂ is recommended for confirmation of endotracheal placement during intubation.
- Monitoring of tidal volumes is the only ventilation monitoring parameter that has been shown to affect outcomes. However, equipment must be shown to be accurate.

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Part V

Indications for Respiratory Support

Educational Aims

- To understand the rationale behind the use of NRS in premature infants
- To know the indications and contraindications of NRS in premature infants
- To know the role of NRS in the delivery room during neonatal resuscitation
- To be familiar with the different modes of NRS and their role in treating the acute phase of RDS and at RDS resolution and for apnea of prematurity
- To understand the rationale and to know how to use surfactant in combination with NRS for the treatment of RDS in the very preterm infants

17.1 The Neonatal Patient

Amir Kugelman

17.1.1 Introduction

The two main indications for respiratory support in preterm infants are respiratory distress syndrome (RDS) and apnea of prematurity.

RDS is the most common respiratory disorder in premature infants, and its incidence and severity increase with decreasing gestational age (Chard et al. 1997). In infants with birth weight between 501 and 1,500 g, more than 50 % have signs of RDS, increasing almost to 90 % in infants below 750 g (Hack et al. 1991).

The major cause of RDS in premature infants is lack of surfactant in the immature lung (Jobe 1993). That immature lung is susceptible to injury by various factors, including mechanical ventilation. Surfactant deficiency results in increased airway surface tension and collapsed alveoli at the end of expiration, atelectasis, uneven inflation, and regional alveolar over distension, which produces epithelial injury and pulmonary edema (Fig. 17.1). Thus, according to the “physiological rationale,” RDS should be treated by two means: (1) exogenous surfactant and (2) gentle support of functional residual capacity (FRC) with continuous positive airway pressure (CPAP).

Surfactant was considered to be the “magic bullet” for treating RDS and reduced mortality of premature infants (Jobe 1993; Soll 1995; Lee

et al. 1999). However, surfactant is administered via endotracheal ventilation, and this by itself can cause lung injury. Despite the new modes of ventilation (such as high-frequency ventilation, volume-targeted ventilation, triggered ventilation, and synchronized ventilation) and the use of surfactant, bronchopulmonary dysplasia (BPD) remains a significant morbidity in premature infants, and its incidence is correlated with the use of mechanical ventilation (Bollen et al. 2007; Greenough et al. 2008; Cools et al. 2010). Thus, ventilator-associated lung injury appears to be related to the duration of invasive ventilation via the endotracheal tube rather than the mode of ventilation. BPD is associated with poor neurological outcome (Majnemer et al. 2000).



Fig. 17.1 Respiratory distress syndrome—chest radiograph

Because mechanical ventilation via endotracheal intubation is associated with BPD, the trend today is to use nasal respiratory support (NRS). NRS is a noninvasive method of maintaining FRC without endotracheal ventilation (Fig. 17.2). NRS includes nasal continuous positive airway pressure (NCPAP) and nasal ventilation.

NRS has been used for the initial treatment of RDS, post-extubation as a “bridge” to spontaneous unsupported breathing, and for the treatment of apnea of prematurity. NCPAP was shown to be effective in treating infants with RDS (Gittermann et al. 1997; Ho et al. 2000; De Klerk and De Klerk 2001). To enhance the potency of NCPAP, it is possible to use nasal intermittent mandatory ventilation (NIMV). The rationale behind the use of NIMV is the administration of “sigh” to the infant, thus opening microatelectasis and recruiting more ventilation units (Lin et al. 1998).

Very premature infants with severe RDS may need the combination therapy of NRS and surfactant to avoid prolonged endotracheal ventilation. This is achieved by the INSURE (INTubation SURfactant Extubation) approach (Verder et al. 1999; Bohlin et al. 2007; Stevens et al. 2007), in which surfactant is administered during brief intubation followed by immediate extubation to NRS.

Term infants with respiratory morbidity (e.g., transient tachypnea of the newborn or meconium aspiration syndrome) may also require NRS. However, there is limited information on NRS in term infants. Thus, our discussion will focus on premature infants.



Fig. 17.2 Nasal respiratory support via nasal prongs

17.1.2 Nasal Respiratory Support During Neonatal Resuscitation in the Delivery Room

Recently, noninvasive ventilation was introduced to the delivery room, as even short duration of endotracheal intubation was shown to be associated with lung damage (Aly et al. 2005). Previous studies have shown that the lowest incidence of BPD occurred in neonatal intensive care units (NICUs) practicing early NCPAP instead of initial mechanical ventilation (Avery et al. 1987), and others reported a multivariable analysis to adjust for baseline risk and showed that most of the increased risk for BPD among VLBW infants resulted from the initiation of mechanical ventilation (Van Marter et al. 2000a).

There is no consensus as to the optimal mode of achieving early lung recruitment in the delivery room. te Pas and Walther (2007) evaluated 207 very preterm infants who were assigned randomly in the delivery room to either a sustained inflation through a nasopharyngeal tube followed by early NCPAP (early functional residual capacity intervention) or repeated manual inflations with a self-inflating bag and mask followed by NCPAP, if necessary, after arrival at the NICU. Needs for intubation, days on mechanical endotracheal intubation, days on NCPAP, air leaks, and moderate to severe BPD were significantly lower when a sustained inflation was used instead of bag and mask ventilation.

Flow-controlled pressure-limited mechanical devices, such as Neopuff Infant Resuscitators (Fisher & Paykel Healthcare Corp. Ltd., Irvine, Calif., USA) to deliver consistent CPAP in the delivery room, are recognized as an acceptable method of administering positive pressure ventilation during resuscitation, especially in preterm infants (Finer et al. 2001). Finer et al. (2001) concluded that the Neopuff, a purpose-built neonatal resuscitator ventilator, facilitates the delivery of the desired airway pressures while maximizing the operator's ability to obtain and maintain a patent airway and facilitates the delivery of prolonged inflations.

Early administration of surfactant and immediate extubation in very preterm infants need to

be considered to achieve a synergistic effect of NRS and surfactant (Sect. 17.1.7).

17.1.3 Nasal CPAP in the Premature Infant

NCPAP is currently a common practice for the treatment of premature infants with RDS (Dunn and Reilly 2003). NCPAP stabilizes the chest wall (Locke et al. 1991), reduces airway resistance (Miller et al. 1990; Gaon et al. 1999), increases FRC (Richardson and Jung 1978; Richardson et al. 1980), reduces obstructive apnea (Miller et al. 1985), and thereby improves lung volumes and oxygenation (Locke et al. 1991; Richardson and Jung 1978).

There are data from animal studies suggesting that CPAP elicits an attenuated inflammatory response in alveolar washes compared to mechanical ventilation (Jobe et al. 2002) and that surfactant treatment followed by CPAP results in less severe morphological lung injury than surfactant together with mechanical ventilation (Nold et al. 2007). Although physiologically appealing and, in parts of the world, associated with positive clinical experiences and outcomes, CPAP as a primary respiratory support option for preterm infants with RDS remains controversial due to lack of data on effectiveness from recent randomized trials (Subramaniam et al. 2005).

NCPAP was shown to be effective in treating infants with RDS and enables the avoidance of mechanical ventilation in a relatively large number of infants (Bollen et al. 2007; Greenough et al. 2008; Davis and Henderson-Smith 2003; Higgins et al. 1991; Kirchner et al. 2005). Morley et al. (2008) studied randomly assigned 610 infants who were born at 25–28 weeks gestation to CPAP or intubation and ventilation at 5 min after birth. In that study, almost half of the infants in the CPAP group required intubation during the first 5 days of life (Morley et al. 2008). Despite that, the odds ratio for death or oxygen treatment at 28 days favored early CPAP over mechanical ventilation. Other outcome measures were similar, apart from pneumothorax, which was increased with CPAP. In the (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD

Neonatal Research Network et al. 2010), 1,316 infants born between 24 0/7 weeks and 27 6/7 weeks of gestation were randomly assigned to intubation and surfactant treatment (within 1 h after birth) or to NCPAP treatment initiated in the delivery room, with subsequent use of a protocol-driven limited ventilation strategy. They found that “death or BPD” in the NCPAP versus surfactant groups did not differ (47.8 and 51.0 %, respectively). NCPAP versus surfactant treatment resulted in less delivery room intubations, postnatal corticosteroids for BPD, fewer days of mechanical ventilation, and need for mechanical ventilation by day 7. The authors concluded that their findings support the consideration of NCPAP as an alternative to intubation and surfactant in preterm infants. These results suggest that even very preterm infants may benefit from early CPAP.

Several centers administer surfactant, immediately extubate the infants, and then use NCPAP (Verder et al. 1999; Bohlin et al. 2007; Dunn and Reilly 2003), in order to shorten the course of mechanical ventilation.

When trying to determine if prophylactic nasal CPAP commenced soon after birth regardless of respiratory status in the very preterm or very low birth weight (VLBW) infant reduces the use of endotracheal ventilation and the incidence of BPD without adverse effects, the Cochrane review (Davis and Henderson-Smart 2003) concluded that there is currently insufficient information to evaluate the effectiveness of prophylactic nasal CPAP in very preterm infants. Neither of the included studies reviewed in that analysis showed evidence of benefit in reducing the use of endotracheal ventilation. The two recent large randomized trials (Morley et al. 2008; SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al. 2010) did not show benefits in terms of reducing BPD in extremely low birth weight infants treated with early NCPAP.

Because the duration of endotracheal mechanical ventilation has a direct correlation with BPD, clinicians are increasingly using NRS to protect the preterm infant’s lungs and allow early extuba-

tion. NCPAP may be used post-extubation and thus decrease the incidence of reintubation (Davis and Henderson-Smart 2003). A meta-analysis of trials, assessing whether CPAP facilitates extubation in 569 infants, demonstrated that use of NCPAP reduced the need for increased respiratory support (defined as if they required higher supplementary oxygen levels than when immediately extubated and, in addition, if the headbox oxygen infants required rescue CPAP). However, NCPAP did not significantly reduce the need for reintubation or influence the oxygen requirement at 28 days (Dimitriou et al. 2000).

Nasal CPAP was used also for the treatment of apnea of prematurity (Davis and Henderson-Smart 2003; Lemyre et al. 2002). CPAP is thought to decrease the frequency of apnea by increasing the FRC and stabilizing oxygenation and/or by splitting the upper airway with positive pressure. NCPAP abolishes obstructive and mixed apnea, but not central apnea (Miller et al. 1985). It may act by distending and maintaining the upper airway rather than by a direct effect on respiratory drive. NCPAP also stabilizes the highly compliant chest wall of the infant by increasing the end-expiratory lung volume, thus improving pulmonary mechanics (Pandit et al. 2001).

NCPAP is effective and has an acceptable safety margin for road-based transportation of infants with RDS. Air transport is feasible, but larger studies are required to assess safety (Murray and Stewart 2008). This conclusion is based on a retrospective study on 220 infants treated with NCPAP, of whom 207 were transported on CPAP of 7 cm H₂O. Thirty infants were transported by fixed or rotary wing aircraft and 190 by road. No infant required intubation or bag and mask ventilation during transport.

17.1.4 Nasal Intermittent Mandatory Ventilation (NIMV) in the Premature Infant

It is possible to enhance NRS by using NIMV. The rationale behind the use of NIMV is the adminis-

tration of “sigh” to the infant, thus opening microatelectasis and recruiting more ventilation units (Lin et al. 1998). In apneic infants, NIMV may improve the patency of the upper airway by creating elevated pharyngeal pressures, and by intermittent inflation of the pharynx, it could activate respiratory drive (Moretti et al. 1999).

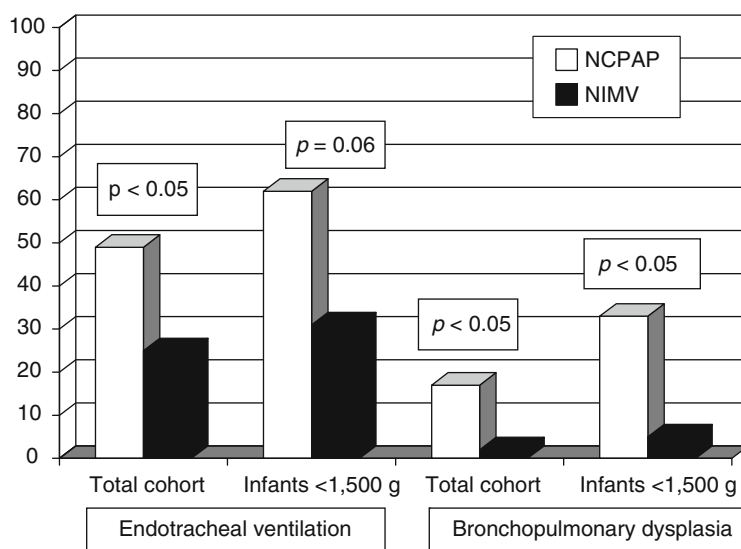
Nasal intermittent positive pressure ventilation (NIPPV) and NIMV are used interchangeably in the literature. The common definition from Davis et al. is NIMV is a method of augmenting NCPAP by delivering ventilator breaths via nasal prongs (Davis and Henderson-Smart 2003). By that definition, NIMV mode is not an assist control mode, where the infant breath triggers a ventilator breath and where the triggering might be of greater importance.

Several investigators have tried to synchronize NIMV with the infant’s breathing by using Infant Star ventilators (Infrasonics, Inc, San Diego, CA) that employed an abdominal pressure-sensing capsule (Davis and Henderson-Smart 2003; Barrington et al. 2001; Khalaf et al. 2001). Moretti et al. found that application of nasal synchronized intermittent mandatory ventilation (NSIMV) was associated with increased tidal volume and minute volume as compared with NCPAP (Davis and Henderson-Smart 2003). NSIMV was shown to be associated with improved thoracoabdominal synchrony and thus

stabilizes the chest wall and improves lung mechanics (Kiciman et al. 1998). NSIMV may have advantages over NIMV. Positive pressure ventilator breaths are delivered only after initiation of respiratory effort by the infants, when the glottis is likely to be open, or after an apneic interval. It was shown that NSIMV compared to NCPAP decreases the work of breathing in premature infants (Aghai et al. 2006). Synchronization of nasal ventilation is problematic especially in small premature infants. The systems are open, and the flows and pressures generated by the premature infants are very small. Also, the abdominal sensor (capsule) may be triggered by motion artifacts other than breathing. While the effectiveness of both pressure-triggered ventilation (Kiciman et al. 1998) and NSIMV (Davis and Henderson-Smart 2003; Kiciman et al. 1998; Aghai et al. 2006) was evaluated, its use was not shown yet to be more beneficial than NIMV.

The first study to use NIMV as a primary ventilatory mode for treatment of RDS was the study of Kugelman et al. (2007). This study showed that NIMV compared to NCPAP decreased the requirement for endotracheal ventilation in premature infants (<35 weeks) with RDS (Fig. 17.3). Failure of NIMV in this study was significantly associated with lower birth weight. Other studies also correlated failure of nasal support with low

Fig. 17.3 Endotracheal mechanical ventilation and bronchopulmonary dysplasia (BPD) in infants treated with NIMV and NCPAP (Reproduced with permission from Kugelman et al.)



birth weight or gestational age (Ammari et al. 2005). Success on NRS depends not only on the severity of RDS, birth weight, and gestational age but also on the experience of medical teams, which is increasing in recent years. Another prospective trial that used NSIMV during the acute phase of RDS just after surfactant administration is the study of Bhandari et al. (2007). They concluded that infants of birth weight 600–1,250 g with RDS receiving surfactant with early extubation to NSIMV had a significantly lower incidence of BPD/death (52 % versus 20 %, $p=0.03$) and that primary mode NSIMV is a feasible method of ventilation in small premature infants. “Too sick” infants were excluded from that study which was more of a feasibility study. The best option for treatment of RDS with respect to gestational age and RDS severity should be further investigated (Dunn and Reilly 2003).

NSIMV was shown to be more effective than NCPAP immediately after extubation in the treatment of RDS (Moretti et al. 1999; Barrington et al. 2001; Khalaf et al. 2001; Friedlich et al. 1999; De Paoli et al. 2003; Davis et al. 2001). Three randomized controlled trials have investigated the effect of NSIMV and NCPAP after extubation (Barrington et al. 2001; Khalaf et al. 2001; Friedlich et al. 1999). All three studies showed that more NSIMV-treated infants remained extubated at 48–72 h. A pooled meta-analysis (159 infants) showed that NSIMV was more effective than NCPAP in preventing failure of extubation [RR 0.21 (0.10, 0.45)] and the number needed to treat was only three infants to prevent one extubation failure (Bhandari et al. 2007; Friedlich et al. 1999). Some infants randomized to NCPAP, and who fulfilled the reintubation criteria, were not reintubated but were given “rescue” NIMV. Eight out of nine of these infants remained extubated. The numbers were too small to detect reliable differences in the rate of BPD, days of supplemental oxygen, or hospital stay (Barrington et al. 2001; Khalaf et al. 2001). Recently, Moretti et al. have shown that by using nasal flow SIMV in infants <1,251 g post-extubation, 94 % (30/32) of infants were successfully extubated as compared to only 61 % (19/31) who received NCPAP ($p<0.005$) (Moretti et al. 2008).

The time of extubation, early or only at RDS resolution, depends on the infants’ gestational age. In 28–34 weeks’ gestation, Santin et al. (2004) showed that infants of 28–34 weeks’ gestational age with RDS requiring surfactant with early extubation immediately postsurfactant to SNIMV had a shorter duration of intubation and decreased need for oxygen as compared to conventional ventilation. There was also a significant decrease in the duration of parenteral nutrition and hospitalization. They concluded that NSIMV/NIMV seems to be safe and effective primary mode of ventilation in larger premature infants. Yet, Bhandari et al. (2007) in a more recent trial found it also correct for small premature infants (600–1,250 g).

NSIMV was shown to be more effective than NCPAP also for apnea of prematurity (Lin et al. 1998; Lemyre et al. 2002). Ryan et al. (1989) randomized 20 premature infants with apnea, on NCPAP, to a 6-h crossover study of NIMV or NCPAP. They did not find any differences in number or severity of apneas. They noted that during some apneas, the peak pressure of 20 cm H₂O did not produce chest movement and postulated that these apneas were due to upper airway obstruction. In 1998, Lin et al. (1998) randomized 34 spontaneously breathing infants with apnea to 4 h of either NCPAP or NIMV. The NIMV group had a significant reduction in the severity and number of apneas (3.5/h to 0.8/h, compared with 2.6/h to 1.5/h in the NCPAP group, $p=0.02$). A meta-analysis of these small trials, regarding apnea of prematurity, suggests that NIMV is more efficacious with apnea that is frequent or severe. However, the studies performed addressed short-term outcomes and as such could not address properly the incidence of requirement for reintubation. Thus, more studies are needed before recommending NIMV as standard of care for apnea of prematurity (De Paoli et al. 2003).

Pressure support ventilation (PSV) is a mode of synchronized ventilation that can supplement the spontaneous breathing effort by assisting each of the infant’s spontaneous breath. A pressure support breath is initiated and terminated in synchrony with the patient’s inspiratory effort.

Due to weak musculature and a compliant ribcage, preterm infants are prone to chest wall distortion during breathing. The underlying lung disease further increases their respiratory workload, and the provision of continuous distending pressure alone is often not sufficient to support their breathing. Thoracoabdominal asynchrony, which occurs because of the negative intrapleural pressure changes transmitted to the highly compliant chest wall of preterm infant, has been suggested to be more effectively reduced by NSIMV compared to NCPAP, perhaps by better stabilization of chest wall (Kiciman et al. 1998). When compared to NCPAP, noninvasive PSV did not increase minute ventilation, but it effectively unloaded the patient's respiratory pump as indicated by a lower inspiratory effort and reduced chest wall distortion (Ali et al. 2007).

17.1.5 Nasal Flow for Premature Infants

Nasal cannulae are frequently used to deliver oxygen. Its use is popular because it allows access to the infant and enables the parents to hold the infant. The mobility is also important in older infants for developmental stimulation. While the method is commonly used in infants with chronic lung disease, the medical teams tend to use it earlier because of its convenience. However, one should be cautious with that use because the amount of oxygen delivered should be controlled (by flow and mixer) and the amount of flow should be controlled as it may cause inadvertent CPAP when the outer diameter of the cannula is 0.3 cm (Santin et al. 2004). Complications reported with the use of high-flow nasal cannula included air leaks (Jasin et al. 2008), gas trapping (Locke et al. 1993), and nasal mucosal injury (Woodhead et al. 2006).

Nasal flow may be indicated as nasal support post-extubation and for apnea of prematurity. Besides oxygen and probably triggering the infant to breathe by the flow itself, nasal flow may provide CPAP (Locke et al. 1993), and this may explain its beneficial effect. When comparing the work of breathing in premature neonates

supported with high-flow nasal cannula (HFNC) and NCPAP, it was found that HFNC provided support comparable to NCPAP (Saslow et al. 2006).

Woodhead et al. showed that HFNC that delivers humid and warm nasal flow, performed better than standard HFNC in maintaining lower respiratory effort score and averting reintubation following endotracheal extubation (Woodhead et al. 2006). Shoemaker et al. (2007), in a retrospective study, reported that HFNC usage increased (64 %) after its introduction in infants of all gestational ages, whereas the usage of NCPAP decreased from 19 to 4 %. They found that comparing the cohort of infants who received either NCPAP or HFNC as an early mode of respiratory support, there were no differences in deaths, ventilator days, BPD, blood infections, or other outcomes. More infants were intubated for failing early NCPAP compared to early HFNC (40–18 %). Use of nasal cannula flow in which CPAP can be delivered with flows exceeding 1 l/min has been suggested as an equivalent treatment modality to NCPAP (Sreenan et al. 2001). Sreenan et al. concluded that nasal cannula at flows of 1–2.5 l/min can deliver positive distending pressure in premature infants and that the HFNC is as effective as NCPAP in the management of apnea of prematurity (Sreenan et al. 2001). However, no randomized prospective study was published yet that compared NCPAP or NIMV versus HFNC.

17.1.6 Contraindications for Noninvasive Respiratory Support

NRS is not possible in a premature infant who needs to be resuscitated with endotracheal intubation immediately after delivery. Endotracheal intubation should be performed in the delivery room if heart rate does not increase to >100 per minute, if the infant has insufficient spontaneous respiratory effort, or if he shows marked and increasing dyspnea (Lindner et al. 1999).

If endotracheal intubation is not required for resuscitation, the neonatal team should decide whether to intubate every extremely premature

infant at risk for RDS immediately and to administer prophylactic surfactant or to consider a trial of NRS. Preventive surfactant administration was shown to be more beneficial than rescue therapy in infants <28 weeks' gestation (Soll and Morley 2001). To note, the included studies in that review were conducted in the context of less than optimal use of antenatal steroids. The impact of prophylactic surfactant may be less dramatic in the setting of increased treatment with antenatal steroids.

Furthermore, it was shown by several investigators that individualized intubation strategy may be safe (Aly et al. 2005; Morley et al. 2008; SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al. 2010; Lindner et al. 1999). Lindner et al. (1999), in a retrospective cohort study, showed that adopting a policy of selective intubation in extremely low birth weight (ELBW) infants resulted in a significantly reduced need for intubation, lower incidence of BPD, intraventricular hemorrhage (IVH), and reduced length of stay. Aly et al. (2005), in a retrospective study, concluded that VLBW infants treated successfully with early NCPAP were unlikely to develop IVH of grade III or IV. Infants who experienced early NCPAP failure were at increased risk for the development of necrotizing enterocolitis. Infants who were intubated briefly in the delivery room were at increased risk for prolonged oxygen requirement. Morley et al. (2008) studied randomly assigned 610 infants who were born at 25–28 weeks' gestation to CPAP or intubation and ventilation at 5 min after birth. In that study, early nasal CPAP did not significantly reduce the rate of death or BPD despite fewer days of endotracheal ventilation as compared with intubation. Yet, apart from increased rate of pneumothorax, there were no other serious adverse events in the CPAP group. Pneumothorax in that study was not associated with long-term pulmonary or neurological outcomes. The SUPPORT study (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al. 2010) also found that NCPAP is a safe alternative in extremely low birth weight infants.

17.1.7 Adjunct Therapies: Surfactant to Avoid Mechanical Ventilation

NRS is an effective mode of treatment for premature infants with RDS, especially in the era of prenatal corticosteroids. Antenatal steroids were found to reduce the rate of RDS (RR 0.66, 95 % CI 0.59–0.73, 21 studies, 4,038 infants) and need for respiratory support (Roberts and Dalziel 2006). Antenatal corticosteroid treatment clearly reduces the incidence of RDS in randomized controlled trials (Crowley et al. 1990; Kari et al. 1994).

Yet, the severity of RDS, the infant's weight and gestational age, and the experience of the medical teams with NRS are significant factors that affect the success of noninvasive ventilation.

Finer et al. (2004) reported that CPAP/PEEP given by Neopuff in the delivery room to ELBW infants did not affect the need for intubation at birth or during the subsequent week. Overall, 20 % of infants did not need intubation by 7 days of life. Aly et al. (2005) reported that the chance of successful maintenance with early NCPAP for >48 h was not demonstrable at <24 weeks' gestation (10 % success). The efficacy of the use of early NCPAP improved significantly by 25 weeks of gestation (45 % success). In the study of (Morley et al. 2008) (gestational ages of 25–28 weeks), 46 % of infants in the CPAP group were intubated during the first 5 days. The intubation rate was 55 % for infants born at 25 or 26 weeks' gestation and 40 % for those born at 27 or 28 weeks' gestation. The median time for intubation was 6.6 h (interquartile range, 2.2–19.3). The reasons for intubation were as follows: a FiO_2 of 0.60 or more (53 % of infants), a PaCO_2 of more than 60 mmHg (8.0 kPa) (41 %), apneic episodes (38 %), or metabolic acidosis unresponsive to treatment (21 %); some infants had multiple reasons for intubation. Another 39 patients in the CPAP group (12.7 %) were intubated after 5 days of age. Thus, while noninvasive ventilation is probably safe, its success depends on gestational age and on RDS severity. Lack of surfactant contributes to NRS failure in the most premature infants.

Surfactant replacement treatment significantly reduces mortality in infants with RDS (Soll 1995). The introduction of surfactant therapy in the USA was reflected in an accelerated reduction in mortality from RDS and was the single most important factor for the decrease in overall neonatal mortality rate in the early 1990s (Lee et al. 1999).

Despite the effectiveness of surfactant treatment in the acute phase of RDS and new ventilation techniques such as high-frequency oscillation and volume-targeted ventilation, bronchopulmonary dysplasia (BPD) remains an important adverse outcome in preterm infants, and its incidence is correlated with use of mechanical ventilation (Bollen et al. 2007; Greenough et al. 2008; Van Marter et al. 2000). Thus, it seems that NRS and surfactant may have a synergistic positive effect in extremely premature infant.

It was shown that combining surfactant with noninvasive respiratory support is beneficial. A recent multicenter study found that when 279 infants, born between 27 and 31 weeks' gestation, were randomly assigned within the first hour of life to intubation, very early surfactant, extubation, and NCPAP (treatment group) or NCPAP alone (control group), the addition of very early surfactant therapy without mandatory ventilation decreased the need for subsequent mechanical ventilation, decreased the incidence of air-leak syndrome, and seemed to be safe (Rojas et al. 2009). Stevens et al. (2007), in a Cochrane analysis, compared two treatment strategies in preterm infants with or at risk for RDS: early surfactant administration with brief mechanical ventilation (less than 1 h) followed by extubation versus later selective surfactant administration, continued mechanical ventilation, and extubation from low respiratory support. They concluded that the first approach was associated with less need for mechanical ventilation, lower incidence of BPD, and fewer air-leak syndromes.

The European CURPAP study is currently evaluating the efficacy of early CPAP and natural surfactant as a combination therapy versus early NCPAP and rescue surfactant for very preterm infants (Sandri et al. 2008). Implementing a strat-

egy of surfactant administration by transient intubation during NCPAP reduces the need for mechanical ventilation (by ~50 %) without adverse effects on outcome and may be an option to more effectively treat RDS, particularly in a care setting where transfer is necessary to provide mechanical ventilation (Verder et al. 1999). Dani et al. (2004) have shown in infants <30 weeks' gestation that the immediate reinstitution of NCPAP after surfactant administration for infants with RDS is safe and beneficial, as indicated by the lesser need for mechanical ventilation and the shorter requirement for respiratory supports, compared with the institution of mechanical ventilation after surfactant treatment. Geary et al. (2008) performed a historical cohort study of appropriately sized preterm infants. Only 1 (1 %) of 87 infants in the pre-early management practice change group received CPAP treatment in the first 24 h of life, compared with 61 (80 %) of 76 infants in the post-early management practice change group. The proportions of infants who required any SIMV during their hospital stays were 98.8 and 59.5 %, respectively. The mean durations of SIMV were 35 days and 15 days, respectively. The combined incidence rates of moderate and severe BPD at corrected gestational age of 36 weeks were 43 and 24 %, respectively. They concluded that successful early management of extremely preterm infants with surfactant treatment followed by CPAP treatment at delivery, lowered oxygen saturation goals, and early amino acid supplementation is possible and is associated with reductions in the incidence and severity of BPD.

Kribs et al. (2008; 2007; 2009) developed a method of surfactant administration during spontaneous ventilation on NCPAP in ELBW infants using thin endotracheal catheter. They reported in a retrospective trial that the choice of NCPAP as initial airway management significantly increased from 69 to 91 % and for NCPAP with surfactant from 75 to 86 %. The rate of NCPAP failure decreased from 46 to 25 %. Survival increased significantly from 76 to 90 %, and survival without BPD rose from 65 to 80 %. No changes in nonpulmonary outcomes were observed.

Perspectives and Future Developments

The current data suggest that in “extremely premature” infants, endotracheal ventilation, surfactant administration, and extubation (immediate or delayed) to NRS may be the preferred approach. The definition of “extreme prematurity” for that decision or for the decision for immediate or delayed extubation is not determined yet and is open for future debate. Furthermore, it relies not only on gestational age and birth weight but also on the severity of RDS, the individual infant condition, and the specific setup in the NICU (time of day, available personnel, etc.). In the future, new effective modes of surfactant administration should be developed that will enable the administration of surfactant without endotracheal intubation and ventilation. There are reports of less invasive surfactant administration through a feeding catheter without intubation (Kribs et al. 2007). Although not yet shown to be effective, aerosolized surfactant may become available in the future.

If NRS is to be tried, NIMV/NSIMV seems to be more beneficial than NCPAP for acute RDS and after extubation, as a “bridge” to spontaneous unsupported breathing. Effective synchronization, pressure support ventilation, and HFV via nasal ventilation (Kugelman et al. 2007; van der Hoeven et al. 1998; Hoehn and Krause 2000) may improve NRS in the future. Extubation with no NRS may be suitable for larger infants. This algorithm needs to be further supported by large, prospective studies in VLBW and ELBW infants.

- In the very preterm infants, combined therapy with surfactant and NRS may be required.
- NIMV is more effective than NCPAP alone for the initial treatment of RDS, after extubation in the recovery phase of RDS, and probably for apnea of prematurity.
- The definition of “extreme prematurity” that mandates intubation and surfactant and dictates immediate or delayed extubation is not determined yet and is open for future debate.

17.2 The Pediatric Patient

Federico Martinon-Torres

Educational Aims

- To provide a comprehensive review of the current indications of noninvasive ventilation (NIV) in children
- To detail pediatric NIV indications in either acute or chronic conditions
- To establish the NIV indication according to physiopathological criteria defining the type of respiratory failure
- To prepare physicians for adequate patient selection (a key factor in NIV success)
- To describe the role of NIV in combination with helium–oxygen mixtures
- To review and discuss NIV contraindications in children

Essentials to Remember

- NRS is an effective treatment of premature infants with RDS.
- It is safe to use a selective intubation approach in the delivery room for premature infants.

17.2.1 Introduction

Noninvasive ventilation (NIV) in the pediatric patient is reasonably safe and efficacious. Owing to constant advances in NIV ventilators and interfaces, as well as the increasing familiarity of

hospital staff with this technique, clinical use of NIV is increasing both in frequency, scope, and efficacy. However, the objective available data supporting its use is limited, the majority of our evidence being extrapolated from adult studies. Data regarding the use of NIV in infants and children are scarce, and case series constitute the majority of our knowledge in both acute and home settings. Furthermore, in many of these studies, different ages and clinical entities are mixed making it more difficult to draw concrete conclusions.

NIV should not be seen as a therapeutic “bridge” between plain oxygen therapy and invasive mechanical ventilation but as the “bridge” to recovery (or wellness) of our pediatric patient without the need of intubation and its related risks and inconveniences. However, it is important to prevent the eagerness to avoid invasive ventilation from unduly delaying endotracheal intubation in those cases where intubation really is necessary. The growing demands that noninvasive ventilation entails for hospital staff require the development of clear indications and treatment guidelines and protocols. Achieving a positive outcome with NIV is dependent on a number of factors; however, the most important of which appears to be patient selection. This chapter aims to review and establish general clinical guidelines and indications of NIV in the pediatric patient based on the existing evidence and author’s experience.

17.2.2 Indications in Acute Respiratory Failure

The indications of NIV in respiratory failure are becoming numerous and increasingly clear, leading to safer and more successful results of the technique. These indications are based on the criteria for pediatric acute respiratory failure (ARF) (Table 17.1). These can be extrapolated to establish a general classification for the different acute and chronic pathologies that can be treated with NIV (Table 17.2). However, from a practical perspective, we consider more useful to classify the

indications according to the type of ARF following physiopathological criteria (Table 17.3):

- Type I ARF. This is characterized by an imbalance between ventilation and perfusion (V/Q mismatch) without alveolar hypoventilation. It first appears as hypoxemia with no increase in arterial carbon dioxide pressure (PaCO_2). Patients may exhibit condensations when examined by chest X-rays.
- Type II ARF. The main feature of type II ARF is alveolar hypoventilation. It is defined by the presence of hypercapnia ($\text{PaCO}_2 > 45 \text{ mmHg}$) with a normal alveolar–arterial oxygen gradient (A-a O_2). Patients may present with hypoxemia due to hypoventilation. Chest X-rays do not reveal any condensations (excluding atelectases).

Based on this classification, the indications of NIV in the pediatric patient are summarized in Table 17.4. Entities such as acute bronchiolitis can be classified under each type of ARF as a function of their clinical characteristics. The use of this guide facilitates the selection of the patient, the choice of the NIV technique and interface, as well as the programming of the initial NIV settings (Fig. 17.4). Out of the absolute

Table 17.1 Criteria for respiratory failure in children

Clinical criteria	Physiological criteria
Weak cough, retention of respiratory secretions	Vital capacity $< 15 \text{ mL/kg}$
Increased use of accessory muscles	Maximum inspiratory force $< 20 \text{ cm H}_2\text{O}$
High respiratory frequency (based on age)	$\text{PaCO}_2 > 45 \text{ mmHg}$ and $\text{pH} < 7.35$
Paradoxical breathing	$\text{PaO}_2/\text{FiO}_2 < 300 \text{ mmHg}$
Incompetent swallowing	$\text{SatO}_2 < 97 \%$ for ambient air
Reduced activity level or diminished function	

Adapted with permission from original table in Medina et al. (2009)

These criteria are not specific for the application of NIV in children; however, they are of great help in patient classification and selection, which is crucial in the NIV outcome (see text)

mL milliliters, *kg* kilograms, *cm H₂O* centimeters water, *mmHg* millimeters mercury, *PaCO₂* arterial carbon dioxide pressure, *PaO₂* arterial oxygen pressure, *Sat O₂* oxygen saturation, *FiO₂* inspired fraction of oxygen

Table 17.2 Pediatric indications of noninvasive ventilation

Acute respiratory failure (ARF)	Chronic respiratory failure (CRF)
A. Decompensated central nervous system (CNS) diseases 1. Apneas in preterm infants 2. Apneas in full-term infants	A. Respiratory sleep disorders 1. Obstructive sleep apnea syndrome (OSAS) 2. Primary or acquired central alveolar hypoventilation
B. Decompensated respiration due to chest wall or spinal abnormalities 1. Obesity–hypoventilation syndrome 2. Prader–Willi syndrome	B. Neuromuscular diseases (NMDs) that affect respiratory musculature 1. Diseases of the 2nd motor neuron (e.g., spinal muscular atrophy [SMA]) 2. Diseases/damage of the phrenic nerve 3. Myasthenia gravis/other congenital myasthenic syndromes 4. Myopathies (e.g., congenital, mitochondrial, metabolic, or inflammatory and deposition diseases) 5. Muscular dystrophies (MDs)
C. Upper airway diseases 1. Infectious etiology (e.g., laryngitis, epiglottitis, tracheitis) 2. Inflammatory etiology (e.g., post-extubation subglottic edema, recurrent or spasmodic croup)	C. Upper airway diseases 1. Tracheomalacia 2. Down’s syndrome (prominent tongue, maxillary hypoplasia) 3. Craniofacial syndromes with mandibular or midfacial hypoplasia 4. Subglottic stenosis 5. Neoplastic etiology (laryngeal or tracheal growths, extrinsic compression of the larynx, trachea)
D. Lung diseases 1. Asthma 2. Bronchiolitis 3. Pneumonia 4. Atelectasis 5. Acute pulmonary edema (APE)	D. Respiratory diseases of the lower tract or parenchyma 1. Bronchopulmonary dysplasia (BPD) 2. Cystic fibrosis 3. Bronchiectasis 4. Diffuse interstitial pulmonary diseases
E. Other situations 1. Apneas after tonsillectomy 2. Postoperative period after corrective surgery for scoliosis 3. Pulmonary complications from sickle cell disease 4. Early extubation 5. Sedation procedures 6. Palliative indication (i.e., severe respiratory failure in terminal illness)	E. Rib cage and chest wall anomalies 1. Progressive scoliosis 2. Asphyxiating thoracic dystrophy (mild forms)
	F. Other situations 1. Spina bifida (pulmonary complications, restrictive lung) 2. Cerebral palsy (laryngeal dystonia, restrictive lung)

Adapted with permission from original table in Medina et al. (2009)

Conditions causing acute or chronic respiratory failure in pediatric patients for which noninvasive ventilation (NIV) is indicated

contraindications (see below), in our opinion, a trial of NIV should probably be offered in time to all forms of acute respiratory failure, considering that with a predominant hypercapnic failure (type II ARF), the patient will be more prone to respond, while in those patients with hypoxemic

ARF (type I ARF), we should have a lower threshold for abandonment of the technique because the chance of success is lower and the risk of overuse higher.

In patients with *acute airway obstruction*, such as that which occurs in laryngitis and in

Table 17.3 Physiopathological classification of acute respiratory failure (ARF)

Type I ARF	Type II ARF
Acute Lung Injury (ALI)	Respiratory center
Acute respiratory distress syndrome (ARDS)	Drugs (opiates, barbiturates, and anesthetics)
Neonatal distress syndrome	Central congenital hypoventilation syndrome (CCHS)
Bronchoaspiration	Upper motor neuron
Acute bronchiolitis	Spinal column trauma
Cardiogenic pulmonary edema	Syringomyelia
Cystic fibrosis	Demyelinating diseases
Pulmonary embolism (air, fat, or blood)	Tumors
Interstitial pulmonary disease	Anterior horn neurons
Postobstructive pulmonary edema	Poliomyelitis
Radiation	Werdnig–Hoffmann syndrome
Sepsis	Lower motor neuron
Severe pneumonia (of bacterial, viral, fungal, or parasitic origin)	Post-thoracotomy lesion of the phrenic nerve
Inhalation of poisons or toxic gases	Guillain–Barré syndrome
Multiple transfusions	Neuromuscular junction
Trauma (pulmonary contusion)	Botulism, multiple sclerosis (MS), and myasthenia gravis
	Antibiotics that block neuromuscular function
	Organophosphorus compound poisoning
	Tetanus
	Pleura and chest wall
	Lesions from chest wall burns with retraction
	Massive pleural effusion and morbid obesity
	Muscular dystrophy (MD) and pneumothorax
	Increased airway resistance
	Obstruction of the larynx (e.g., laryngitis, diphtheria, epiglottitis, aspiration of foreign bodies, post-extubation edema, and paralysis of the vocal chords)
	Lower airway obstruction (e.g., emphysema, asthma, and acute bronchiolitis)

Adapted with permission from original table in Medina et al. (2009)

The author considers this classification the most practical in order to indicate NIV in the pediatric patient. Note that there are entities such as bronchiolitis that may fit in both columns according to the predominant pattern

certain pharyngeal–tonsillar infections, NIV can markedly reduce the muscle effort required for breathing and improve gas exchange. It must be noted that use of NIV here is not devoid of risks and should be performed in the presence of experts in managing complicated airways, with adequate material available for establishing a definitive airway and only if the patient maintains their physiological reflexes for airway protection.

For ARF related to *bronchiolitis*, NIV can be indicated at different moments and for different reasons. For the youngest patients, who present

with apneas, CPAP tends to be indicated as in the case of apneas in preterm infants. Patients tend to respond favorably, except in the case of severe apneas and/or if the infection evolves into pneumonia. NIV then takes on the same indications and limitations described for severe cases of hypoxemia. For patients with obstructive respiratory failure, with an increase in respiratory muscle effort as well as secondary retention of CO₂, NIV with two levels of pressure (bi-level positive pressure airway ventilation, or BiPAP) tends to be indicated, namely, for improving gas exchange and reducing respiratory effort. Nonetheless, a

Table 17.4 Objectives of long-term home noninvasive ventilation

(a) Maintain and prolong the patient's life
(b) Improve the quality of life of the patient and their family
(c) Maintain adequate (i.e., age-appropriate) growth and development of the patient
(d) Promote lung growth and expansion, and prevent chest wall deformities
(e) Reduce morbidity
(f) Facilitate return of the patient into their family circle
(g) Optimize the cost to benefits ratio of the patient's healthcare

recent random study which demonstrated that use of CPAP alone was sufficient to improve hypercapnia warrants mention. The benefits of NIV employing mixtures of helium and oxygen in severely affected patients are also noteworthy (see section below). The greatest challenge in this type of pathology resides in the fact that adequate material is often difficult to find for these patients (typically, infants younger than 3 months).

Indication of NIV in pediatric patients with severe hypoxemia due to *asthma* remains highly controversial. The complications implied in conventional mechanical ventilation (CMV) for this pathology have led to the search for alternate ventilatory strategies. NIV has been shown to improve oxygenation in patients during severe asthmatic attacks. NIV treatment of children with this pathology has scarcely been studied, and the few existing reports deal with small patient populations: 33 (Mayordomo-Colunga), five (Carroll), and three (Akingbola). Nonetheless, in the study by Mayordomo-Colunga, NIV only failed in one case. This is accomplished through a minor adjustment of the V/Q mismatch, whereby using a PEEP which does not exceed 80–90 % of the auto-PEEP in combination with an inspiratory positive airway pressure (IPAP) or a pressure support (PS) that lowers the level of respiratory effort required to maintain an adequate flow volume for gas exchange. The greatest challenge in clinical practice is to ensure that the patient couples well to the ventilator, without any agitation;

this often requires light sedation. However, in respiratory failure with hypercapnia due to an asthmatic attack, NIV has not proven superior to CMV nor has it been shown to lead to lower number of required intubations. Early administration of NIV (i.e., before total respiratory failure) and use of ventilators that are very sensitive to the respiratory efforts of the patient and that consequently enable good synchronization may be important factors in the success of the treatment.

Indication of NIV in severe hypoxemic respiratory failure (i.e., $[\text{PaO}_2/\text{FiO}_2] < 300$), such as that which occurs in *ARDS* or in *acute pulmonary lesions* (ALI), is also the subject of intense debate. The majority of studies on adult patients do not differentiate among the different causes of ARDS (i.e., whether it is primarily pulmonary or systemic) nor do they distinguish between ALI of infectious or traumatic origins. Currently, the most widely accepted conclusion is that NIV cannot be recommended universally for ARDS patients ($[\text{PaO}_2/\text{FiO}_2] < 150$); rather, it should be reserved for hemodynamically stable patients without metabolic acidosis and should only be administered in an ICU by staff with NIV expertise. In a recent study of adults, the authors observed that up to 54 % of patients with ARDS that had initially been treated with NIV did not require intubation. They also reported that a $(\text{PaO}_2/\text{FiO}_2)$ value > 175 after 1 h of NIV is indicative that the treatment will be successful and stated that for patients with $(\text{PaO}_2/\text{FiO}_2) < 175$, NIV must be considered even if all the intubation criteria are not strictly met. Patients who benefitted from NIV had significantly less complications, especially those of an infectious nature, and required fewer days in the ICU compared to patients treated from the beginning with endotracheal intubation and mechanical ventilation. Few promising studies on severely hypoxemic pediatric patients exist, and no universal guidelines have yet been established for this pathology. It seems reasonable to extrapolate the findings from adult patients and then proceed cautiously in the most severe pediatric patients (according to the level of severity upon admission), without delaying intubation in those patients who, after 1 h of treatment, do not exhibit any clinical or blood gas improvement.

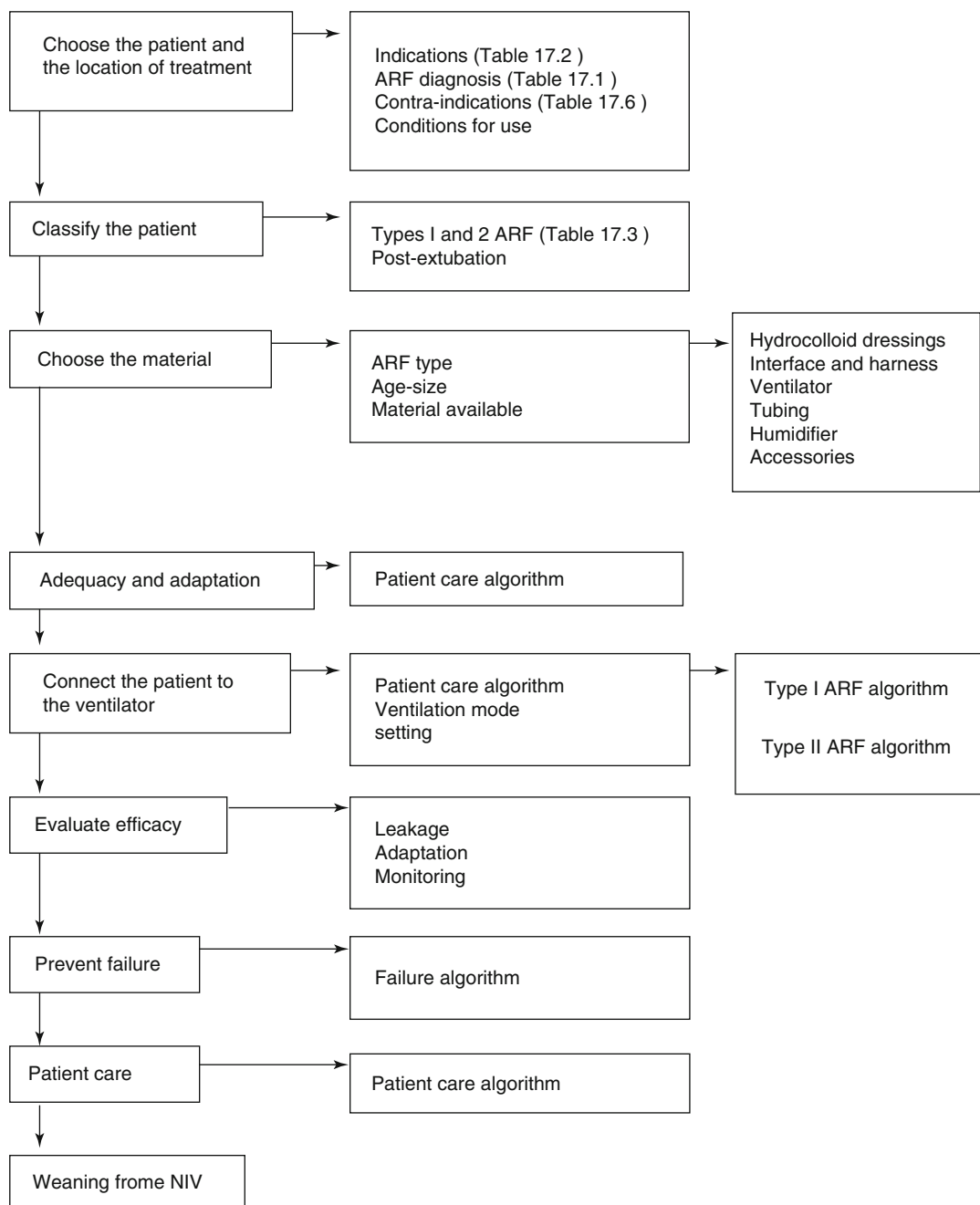


Fig. 17.4 General algorithm for noninvasive ventilation (Adapted with permission from original table in Medina et al. (2009))

Among situations of ARF in adult patients, use of NIV is probably most well documented for *acute pulmonary edema* (APE). NIV, in either CPAP or BiPAP modes, has been shown to rap-

idly improve gas exchange and lead to lower intubation and mortality rates and is relatively cost-effective. NIV in APE currently tends to begin in the ER and is even used during

extra-hospital transport. APE is much less frequent in pediatric patients than in adult patients, owing to the rarity of cardiac ischemia in the pediatric age. *Cardiogenic acute pulmonary edema* (CAPE) may be the first sign of severe cardiac insufficiency (e.g., myocarditis, cardiomyopathy, or a congenital deformation). In this case, if there is any clear cause of hemodynamic instability, then NIV must be used cautiously, in the PICU and with strict monitoring. Conversely, if the APE is due to hypervolemia during an acute decompensation of a known and controlled cardiac condition that arises in the postoperative period of corrective cardiac surgery, then NIV, owing to its mildness, should be attempted as the first treatment option in tandem with the specific medical treatment. Among noncardiogenic edema, a noteworthy type is that of *APE due to negative intrathoracic pressure*, which is caused by a spontaneous forced respiration against an obstruction in the upper airway. This scenario has been reported in patients after ear, nose, and throat (ENT) surgery. In these cases, in which the mechanism appears to be an increase in permeability due to a change in pressure in the pulmonary arterioles and capillaries, if the airway is permeable and safe, then the response to NIV tends to be very good and the patient tends to improve within a few hours. Lastly, if the edema is found within the context of an ALI (e.g., due to inhalation of toxic material, infection, or trauma), then the level to which the pulmonary parenchyma has been affected and the grade of the hypoxemia should be evaluated as described above for ARDS.

During the course of *neuromuscular diseases* (NMDs), affection of respiratory muscles leads to progressive chronic respiratory failure, although this still allows the patient to maintain a certain minimum quality of life. However, in the presence of a precipitating factor—typically a respiratory infection, convulsions, medical intervention, or an intercurrent illness which further limits daily physical activity or demands greater muscle effort—ARF arises, primarily via alveolar hypoventilation. In a recent study, NIV was shown to be a safe and effective first line of treatment for infants and children suffering from

NMD. The authors of the study emphasize the importance of recognizing patients who can maintain sufficient respiration without use of a ventilator, whom they consider as ideal candidates for NIV, given that conventional mechanical ventilation (CMV) via endotracheal intubation with sedation and analgesia would further weaken respiratory muscles, complicate weaning, and often imply definitive tracheotomy. They even propose that use of conscious sedation to facilitate coupling of the NIV interface to the patient should be considered before ruling out NIV.

Similarly to the case of NMDs, *diseases of the chest wall and of the spinal cord* imply a restrictive form of respiratory failure and a high propensity to atelectasis. In these cases, NIV is not only utile during flare-ups but also during the perioperative period of surgery to correct thoracic defects, facilitating weaning from mechanical ventilation.

Indication of NIV to *facilitate extubation and prevent reintubation* in adult patients is currently accepted by the majority of authors. Patients who could most benefit from use of NIV after extubation or even after decannulation are those with chronic lung disease. Hence, the typical pediatric patient who could benefit from NIV would be a preterm infant who has undergone tracheal intubation for administration of surfactant, for whom extubation may be advised to diminish any side effects of mechanical ventilation on their immature lungs. In the pediatric patients, indications are analogue to those in the adult patient, and NIV may be particularly useful after prolonged intubation.

NIV has also proven effective for ARF in patients who have undergone *autologous bone marrow transplant*. The efficacy of NIV for this patient group is limited to certain etiologies such as APE following hyperhydration before a chemotherapy session. More severe etiologies (e.g., pulmonary hemorrhage) call for intubation and CMV. NIV seems to involve fewer complications than CMV. NIV has likewise proven useful in pediatric ARF patients affected by *oncological pathology*, with recent results like those published by Pancera, encouraging its use as a first-line treatment in children with malignancies who

develops acute respiratory failure with the exception of those with severe hemodynamic compromise.

Finally, the *palliative indication of NIV* in pediatric patients should not be forgotten. In these patients, NIV can improve an intercurrent process or just ease symptoms of respiratory difficulty.

17.2.3 Indications in the Child with Chronic Pathologies

In the case of chronic pediatric pathologies, the indications of NIV comprise two main groups: (a) pathologies that can be clinically improved (e.g., bronchopulmonary dysplasia [BPD] and laryngotracheomalacia) and (b) those which are stable or progressive (e.g., NMDs and congenital central hypoventilation syndrome [CCHS]). These indications are linked in many cases to the possibility of starting or improving home respiratory care which itself means higher quality of life for these children (Table 17.5). NIV has several indications in the child with chronic pathologies that may be summarized according to different classifications (see Tables 17.2 and 17.4).

Upper airway obstruction facilitated by atony of the airways may occur in sleeping children with anatomical alterations or malformations (e.g., hypertrophy of the tongue or of the tonsils and palate) or with conditions marked by increased upper airway resistance (e.g., underdevelopment or repositioning of the jaws, narrow palate, large soft palate, or abnormal airway curvature at the base of the skull). Although some of these patients may be treated with surgery, they can also benefit from temporary NIV. In children with *craniofacial anomalies*, hypoxemia or hypercarbia secondary to airway obstruction may have deleterious effects on their neurological development. Indeed, many of these patients suffer from hyperactivity or major delays in growth and development.

Laryngotracheomalacia can cause severe complications such as airway obstruction, leading to sudden death, pulmonary hypertension, cor

pulmonale, stunted growth, and delayed intellectual development; however, most children overcome this condition by age two. Surgery (e.g., epiglottoplasty) may not be sufficient for some patients. However, before hospital personnel consider treating these patients by tracheotomy, which is associated with a high degree of morbidity, they should consider NIV, which reduces work of breathing. EPAP frees blocked airways and keeps the upper airway open and increases the FRC, which in turn dilates the pharynx. NIV may be similarly advantageous for lower airway malacia disorders.

In patients with a lung disease involving limited pulmonary reserve, the normal effects of sleep on respiration can lead to clinically significant ventilatory and gas exchange anomalies. Cystic fibrosis, bronchiectasis, bronchopulmonary dysplasia (BPD), and diffuse interstitial pulmonary diseases are all exacerbated during sleep, especially due to hypoxemia during REM sleep. The first use of NIV for *cystic fibrosis (CF)* patients was only as temporary support during lung transplants. However, its indications for this disease have since expanded to encompass treatment of symptoms including acute hypercapnia and respiratory muscle fatigue and to assist in kinesitherapy for improving diminished oxygen saturation. Late-stage CF patients develop hypoxemia and hypercapnia, especially during sleep. Gozal demonstrated that NIV markedly improves alveolar ventilation during sleep compared to oxygen therapy alone. The same author also demonstrated that NIV improves subjective feelings of dyspnea, facilitates performance of everyday tasks, and increases tolerance of respiratory kinesitherapy. The impact of NIV in CF lung function remains to be proved.

Bronchopulmonary dysplasia (BPD) causes respiratory failure of varying degrees which can become aggravated during sleep but which gradually improves. BPD patients are typically treated with oxygen therapy and, in some cases (e.g., to correct hypoxemia), by ventilation via nasal interface. Long-term hypoxemia during growth stages can cause pulmonary hypertension and, ultimately, cor pulmonale and can lead to poor weight gain.

Table 17.5 Indications of noninvasive ventilation in chronic pediatric pathologies

1. Pathologies of the respiratory system
1.1. Airway
1.1.1. Craniofacial malformations
1.1.1.1. Retrognathia
1.1.1.2. Micrognathia (e.g., Treacher Collins and Pierre Robin syndromes)
1.1.1.3. Hypoplasia of the midface (e.g., Pfeiffer, Crouzon, and Apert syndromes)
1.1.1.4. Macroglossia (gigantism syndrome)
1.1.2. Major hypertrophy of the adenoids and of the tonsils and/or soft palette
1.1.2.1. Temporary or permanent contraindications to surgery
1.1.2.2. Sick cell disease
1.1.2.3. Respiratory tract malacia
1.2. Lung diseases
1.2.1. Cystic fibrosis
1.2.2. Bronchiectasis
1.2.3. Bronchopulmonary dysplasia
1.2.4. Diffuse interstitial pulmonary diseases
2. Neurological diseases
2.1. Central
2.1.1. Congenital
2.1.1.1. Central hypoventilation syndrome (primary)
2.1.1.2. Type II Arnold–Chiari malformation
2.1.1.3. Leigh syndrome
2.1.1.4. Moebius syndrome
2.1.1.5. Carnitine deficiency
2.1.1.6. Pyruvate kinase deficiency
2.1.2. Acquired (asphyxia, infections, trauma, tumors...)
2.2. Peripheral
3. Neuromuscular and chest wall diseases
3.1. Motor neuron (Spinal muscular atrophy...)
3.2. Peripheral nerve (phrenic nerve lesions, Charcot–Marie–Tooth syndrome...)
3.3. Neuromuscular junctions (myasthenia gravis or congenital myasthenia)
3.4. Musculares
3.4.1. Dystrophinopathies (Duchenne and Becker syndromes)
3.4.2. Non-dystrophinopathies
3.4.3. Myotonic dystrophy
3.4.4. Congenital myopathies
3.4.5. Metabolic myopathies
3.4.6. Mitochondrial myopathies
4. Mixed pathologies
4.1. Down’s syndrome
4.2. Mucopolysaccharidosis
4.3. Prader–Willi syndrome
4.4. Achondroplasia
4.5. Obesity–hypoventilation syndrome
5. Miscellanea

Alveolar hypoventilation is nearly exclusive of patients with neuromuscular or lung diseases, and it can be classified as congenital or acquired.

In the former case, it can be secondary to brain malformations (e.g., type II Arnold–Chiari malformation) or functional anomalies (e.g., pyruvate

kinase or carnitine deficiencies). Children with *central hypoventilation syndrome* (CCHS) normally require ventilatory assistance during sleep, and the most severe cases may also require it during the day. In the past, all pediatric patients were initially tracheotomized, and those patients treated with primarily nocturnal hypoventilation were then transitioned to NIV. NIV is now used increasingly more often and in ever younger patients. Children with severe CCHS may require a diaphragmatic pacemaker during the day, to improve their mobility, and NIV during sleep. Whatever ventilation mode is used, the primary objective is to prevent episodes of hypoxia and their consequences on cardiopulmonary (e.g., hypertension) and cerebral (e.g., convulsions and mental retardation) function. Indeed, the prognosis for these patients can be improved if hypoxia can be avoided.

Type II Arnold–Chiari malformation is the form of this complex deformation which is most related to respiratory sleep disorders. Compression of the spinal cord can cause central apneas due to reduced response to hypercapnia or by affecting the peripheral response to hypoxia via compression of the ninth cranial nerve. Obstructive sleep apnea may result from vocal cord abductor paralysis (VCAP) or from compromised function of the pharyngeal dilator muscle caused by lesions in the ninth or tenth cranial nerve. Decompression of the posterior fossa is the first treatment strategy employed for Arnold–Chiari syndrome. However, this may not be sufficient, especially in patients with obstructive sleep apneas; NIV would then be required.

Respiratory failure is often a major cause of morbidity and mortality in acute and chronic *neuromuscular disease* (NMD) patients, although this varies highly according to the pathology. Hence, respiratory failure in NMD patients with normal lungs may cause hypoxemia and hypercapnia comparable to that found in severe lung diseases. NMD patients have difficulty breathing primarily because they cannot expand their chest wall (i.e., lungs, rib cage, and diaphragm). Respiratory complications caused by NMD have been known for quite some time; however, they are often underestimated and occur more frequently than assumed.

The role of sleep in these complications was only recently discovered, and the imitations that NMDs place on respiratory musculature start during sleep and continue during waking hours. All NMDs may imply secondary conditions such as scoliosis or pulmonary hypoplasia, which in turn contribute to the development of atelectasis, respiratory infections, and respiratory failure (and consequently, all of the aforementioned problems). Hence, these NMD patients ultimately require NIV during sleep. Medical and technological advances in NIV have fomented use of home mechanical ventilation, which in turn has led to new approaches to many NMDs that were previously considered fatal without exception. Home NIV together with aggressive measures to improve cough clearance has increased the life expectancy of pediatric NMD patients and improved their quality of life.

There is a general consensus that NIV is beneficial for all *spinal muscular atrophy* (SMA) patients except those with type I. Early NIV treatment has been proposed for stimulating development of the chest wall and growth of the lungs. Prophylactic use of NIV (i.e., before symptoms of hypoventilation appear) favors chest wall development and may even reduce symptoms, especially in children with type II. However, the prognosis for each child should be determined on an individual basis and not according to their type of SMA.

Pulmonary function in *muscular dystrophy* (MD) patients is characterized by three phases: In the first, up to age ten, the patient has normal lung growth and development; in the second, pulmonary function begins to plateau and the patient begins to lose muscle strength; and in the third, the patient suffers a gradual loss of forced vital capacity. The first signs of diminished respiratory function in MD patients appear during sleep: obstructive sleep apneas, in younger children, and then hypoventilation, later on. In one study, NIV treatment led to significant improvements in nocturnal blood gas exchange, but it did not affect sleep patterns, strength of respiratory musculature, number of hospitalizations, or rate of invasive ventilation. In contrast, another study reported a lower number of hospitalizations

among patients treated with NIV compared to those treated by tracheostomy. Long-term NIV does not appear to be beneficial. Consequently, the early introduction of NIV in children with Duchenne muscular dystrophy seeks to ameliorate nocturnal hypoventilation, thereby improving daytime CO₂ elimination. The explanation of this change is unclear, with studies suggesting that this nocturnal NIV might restore daytime brainstem responsiveness to elevations in PaCO₂. In myopathies and congenital MDs, the level of muscle weakness and its limitations on respiratory function are related to the myopathic or dystrophic process. In some cases, NIV may prove insufficient, and the patient must be switched to CMV by tracheostomy.

Respiratory difficulties may also be caused by complex mixed etiologies. The particular facial characteristics of children with *Down's syndrome* are partially due to their abnormal cranial structure. This malformation, combined with the fact that Down's syndrome patients have narrow upper airways, suffer from glossoptosis or macroglossia, and are predisposed to other conditions (e.g., obesity, hypothyroidism, and generalized hypotonia), leads to a 30–50 % higher rate of obstructive sleep apnea syndrome (OSAS) in children with Down's syndrome as compared to healthy children. Pulmonary hypertension induced by airway obstruction occurs more quickly in children with Down's syndrome, as it is facilitated by other factors such as pulmonary hypoplasia, congenital cardiopathy (in 30–40 % of patients), and recurrent respiratory infections. OSAS often goes unnoticed by hospital staff and patient's families: many of its sequelae (e.g., growth, alterations in behavior or sleep, and pulmonary hypertension) are often confused with effects of the syndrome itself. Airway obstruction in Down's syndrome patients is usually caused by hypertrophy of the tonsils and adenoids; therefore, it is often treated by surgical resection of the affected tissue. However, patients that do not suffer this hypertrophy or for whom surgery does not provide the desired results must be treated with NPPV. Good results have been reported for home NPPV via nasal mask.

Patients with *mucopolysaccharidosis (MPS)* often suffer from compromised respiratory

function: their tongue, nasal mucous membranes, oropharynx, epiglottis, tracheal wall, and bronchi become enlarged, ultimately leading to total obstruction of the airways. This progressive process is associated with the characteristic cranial shape of MPS patients, which favors recurrent respiratory infections as well as airway obstruction, which can be severe and cause OSAS. MPS patients also suffer from bone malformations (e.g., scoliosis, hyperkyphosis, thoracolumbar gibbosity, and/or lumbar hyperlordosis) that can affect respiratory function. The extent of respiratory compromise depends on the type of MPS: the most severe consequences occur in type I (Hurler syndrome) and type II (Hunter syndrome). These patients are particularly difficult to intubate; furthermore, due to their spinal column abnormalities, they must be intubated with extreme caution. The multifaceted etiology of these patients complicates their treatment. In the past, sleep apneas in these patients were treated by tonsillectomy and/or adenoidectomy. However, due to the diffuse affection of the airway and to the continuous local deposits of polysaccharides that occur in MPS, these approaches are only temporary solutions. Hence, NPPV has become the preferred method for long-term efficacy.

Respiratory problems in *Prader–Willi syndrome* have a mixed etiology, encompassing peripheral and central mechanisms: muscular hypotonia, reduced lung function, facial dimorphism with arched palate and narrow airways, hyperplasia of the tonsils and adenoids, obesity, and malfunctioning of the hypothalamus and of chemical receptors. NIV is a common treatment for Prader–Willi patients with respiratory sleep disorders; however, it is often difficult to administer due to the behavioral perturbations that frequently accompany the syndrome.

Achondroplasia patients are predisposed to respiratory sleep disorders (including sudden death) through various mechanisms: mechanical (tonsils and adenoids hypertrophy, hypoplasia of the middle third of the face), neurological (brain stem compression due to stenotic foramen magnum), and restrictive (small chest wall). The relative severity of each respiratory condition may

vary with the phenotype of achondroplasia, and NIV indication should be adapted accordingly.

Importantly, NIV for chronic conditions is being progressively indicated in younger patients, and we must be aware of the effects of the mask pressure on the child's face and the risk of facial deformation being high. Children's facial bones are constantly growing and highly moldable; by age four, only 60 % of the facial structure has been formed. The risk of facial deformation in long-term application of NIV is very high in young children that use it several hours per day (e.g., CCHS patients).

17.2.4 Modes of Application and Indications

Presently, noninvasive positive pressure ventilation with two levels of pressure tends to be the preferred mode for initiating NIV in children in nearly all cases, with the exception of certain pathologies that can initially be treated with CPAP alone (e.g., acute pulmonary edema).

17.2.4.1 CPAP

CPAP is the simplest NIV mode and consists of the maintenance of a continuous positive pressure throughout the respiratory cycle. This pressure is delivered via continuous airflow and/or a pressure valve, enabling the patient to breathe spontaneously. In this mode, the child determines the respiratory frequency and tidal volume according to the breathing work. The continuous pressure in CPAP keeps the airway open, increases the respiratory functional capacity, and reduces alveolar collapse. CPAP can be administered through any interface and using various systems and ventilators which may influence the outcome. An ideal CPAP system would administer continuous flow (at least two to three times the normal minute volume) such that the patient could breathe and draw in air at will and would monitor at least pressure, volume, and respiratory frequency.

CPAP is indicated mainly in children with respiratory failure without marked hypoventilation (pneumonia, chest wall trauma, cardiogenic pulmonary edema), obstructive sleep apnea syn-

drome (OSAS), central and/or obstructive apneas in premature/ex-premature infants with bronchiolitis, post-extubation respiratory failure, and respiratory failure with weak respiratory effort (if BiPAP is not available).

CPAP is simple, easy to use and adjust, and can be delivered with a simple apparatus. However, CPAP has disadvantages: (1) It does not assist the patient with each breath, (2) it does not provide safety breaths for patients who are hypoventilating or have constant apnea (hence, monitoring of cardiorespiratory signals and of transcutaneous oxygen levels is crucial), and (3) use of excessive CPAP can lead to pulmonary overinflation (infants with bronchiolitis are at especially high risk) and diminished venous return.

17.2.4.2 Noninvasive Positive Pressure Ventilation

Noninvasive positive pressure ventilation may be performed with either specific NIV devices or using conventional invasive ventilators under volume control or pressure control. The former option of NIV is indicated for hospital use when volume-controlled or pressure-controlled methods are required and when an NIV ventilator with built-in oxygen blender is either unavailable or unable to provide good ventilation or adaptation to the patient. Nearly any ventilation method or mode can be used, but the advantages and disadvantages of each method or mode to deliver NIV are similar to those for delivering invasive ventilation. In volume-controlled methods, the pressure is variable and there is a higher risk of leakage, with lower tolerance by the patient as well as gastric distension, and skin irritation and/or necrosis. When pressure-controlled methods are applied, leaks and tolerance are considerably enhanced compared to volume-controlled modalities, and the air distribution is also better thanks to the decelerating flow. However, if the patient's resistance or compliance changes, a sufficient ventilation cannot be guaranteed. Pressure support ventilation (PSV) is the method that better provides adaptation to the patient; however, air leakage can extend the inspiratory flow even after the patient has started expiration. NIV modes

with conventional ventilators have the main disadvantage of a worse adaptation in BiPAP mode compared to NIV ventilators as well as not providing sufficient leak compensation, particularly in pressure- or volume-controlled modes.

The *noninvasive ventilation modality with continuous flow and bi-level positive airway pressure* is available in NIV ventilators and in some conventional ventilators that have an NIV module. In this mode, a turbine generates pressure at two levels (inspiratory positive airway pressure [IPAP] and expiratory positive airway pressure [EPAP]) with a continuous flow throughout the respiratory cycle. Although it is traditionally known as BiPAP (bi-level positive airway pressure), there are legal issues concerning use of this acronym; hence, this mode is given a different name by each manufacturer. This is the most widely used NIV mode for all types of patients and clinical scenarios. The ventilator constantly monitors the patient's respiratory effort, using a highly sensitive flow sensor attached to the circuit, which enables synchronization with spontaneous breathing as well as compensation for any leaks in or near the mask. The oldest BiPAP ventilators can be programmed in three different modes:

- (a) Spontaneous (S mode). This is in fact equivalent to pressure support with constant flow. The ventilator maintains a CPAP (EPAP) until the patient draws in, at which point it switches to a pressure support (IPAP). The frequency and duration of the inspiration are controlled by the patient. The patient triggers all inspirations, and the ventilator helps the patient with each breath.
- (b) Spontaneous/timed (S/T) mode. The ventilator acts as pressure support for the patient's spontaneous breaths. If the patient does not trigger a minimum number of respirations, then the ventilator runs a cycle comprising an IPAP, an inspiratory time, and an EPAP at a programmed frequency. S/T is the most widely used bi-level mode for both acute respiratory failure (ARF) and chronic respiratory failure (CRF) patients.
- (c) Timed (T) mode. The ventilator delivers a programmed number of breaths regardless of

the patient's respiratory efforts. This mode—not available in the latest NIV ventilators—should only be used if the ventilator cannot detect the patient's breath.

The NIV ventilators offer clear advantages over any other device for NIV, providing better adaptation and leak compensation. Even so, triggers are not always sensitive enough for the youngest children, and the flow required to reach the programmed pressure may occasionally be badly tolerated.

There are other mixed ventilation modes—although with little if any supporting evidence for their use in pediatric patients—in which ventilation is controlled by volume but regulated or cycled by pressure (average volume-assured pressure support (AVAPS) of Respironics BiPAP® or guaranteed volume of Draeger). Theoretically, these modes ensure ventilation with low risk of hypoventilation or hyperventilation, but there is no experience with pediatric patients. Another mode of NIV is proportional assist ventilation (PAV) which is a partially synchronized mode in which the ventilator delivers a variable pressure support and flow which are instantly adjusted according to the patient's respiratory effort. The scarce amount of clinical experience with this modality precludes any specific pediatric indication with the exception of some cooperative older children.

In summary, among available NIV modes, double pressure modes with continuous flow seem to be the best tolerated by patients. However, there have been very few comparative studies on the efficacy and tolerance of different NIV modes, none of which have dealt with pediatric patients. Accordingly:

- (a) *For acute respiratory failure patients.* Bi-level pressure (S and S/T), assisted/controlled, PSV, and PAV (only studied in adults) have all been shown to improve minute ventilation, reduce respiratory frequency and breathing work, and improve blood gas levels, thereby lowering intubation rates. However, no study has shown either of these modes to be superior. In the particular case of cardiogenic acute pulmonary edema, the most widely used modes are CPAP and S/T, as they decrease the respiratory

frequency, correct the respiratory acidosis, and improve hemodynamics.

- (b) *For chronic respiratory failure.* The preferred NIV mode or method widely varies according to the subjacent pathology and the patient's particular conditions as seen above. Cystic fibrosis is most often treated with PSV. Restrictive pulmonary disease and central hypoventilation are managed with volume-controlled methods. Obstructive sleep apnea is better managed with CPAP or bi-level pressure ventilation.

17.2.5 Contraindications for Noninvasive Respiratory Support

Few absolute contraindications exist for noninvasive ventilation, being severe neurological impairment and significant hemodynamic instability being the only two repeatedly included in all articles, protocols, and textbooks. With improvement not only in knowledge and team experience but also in technical advances for the performance of NIV (better equipments and interfaces mainly), the list of contraindications is being constantly updated. Indeed, certain conditions that only a few years ago were considered absolute contraindications are now considered just relative (e.g., pneumothorax or recent gastric surgery). Moreover, the British Thoracic Society guidelines accept the use of NIV for patients with contradictions as long as intubation is planned or the treatment is only palliative.

Nonetheless, there are certain conditions that constitute absolute contraindications that must be carefully evaluated (Table 17.6). Among them, the following should be outlined:

- (a) *Airway protection required.* In any situation in which airway protection is indicated (e.g., coma or active digestive hemorrhage), NIV is absolutely contraindicated, since, as with use of a laryngeal mask, it cannot guarantee this protection. The only exception to this rule is for patients with hypercapnic encephalopathy, who can derive neurological benefits from a short (2–3 h) test treatment of NIV.
- (b) *Severe respiratory failure.* Contraindication of NIV in severe respiratory failure is supported by data on adult patients: A higher mortality rate has been observed in patients that received intubation after preliminary NIV treatment. However, patients for whom intubation is not a valid option due to the causative disease (e.g., palliative use in terminal patients) are an exception. Particularly, in ARDS setting, a $\text{PaO}_2/\text{FiO}_2$ ratio <150 indicates a high risk of NIV failure, and hence, NIV should generally be considered contraindicated.
- (c) *Fixed obstruction of the airway.* NIV is probably contraindicated in these situations, which take too long to resolve the underlying condition. Otherwise, NIV may be considered a “bridge” to avoid intubation in those cases where specific therapy for the obstruction exists and is planned within a reasonable time frame.
- (d) *Abundant and thick secretions.* Restricted access to cleaning the airway—especially in the case of an oral–nasal interface in patients with limited coughing ability—is a high-risk factor for NIV failure.
- (e) *Vomiting.* As with abundant secretions, the presence of vomit makes maintaining a well-positioned interface for continuous administration of NIV nearly impossible.
- (f) *Hemodynamic instability and shock.* For these patients, the concept of energy conservation should be applied and thus respiratory effort eliminated. In postoperative cardiac patients, the presence of arrhythmias can often be considered a relative contraindication for NIV.
- (g) *Craniofacial malformations, trauma, and burns.* Any interference or impracticality to put and/or hold the interface in the right position precludes any option to NIV. Moreover, positive pressure in the presence of ethmoidal fractures has been associated with orbital herniation. Some authors have postulated that application of NIV in patients with cerebrospinal fluid (CSF) fistulae implies an increased risk of post-traumatic meningitis, but this claim remains unproved.

Table 17.6 Contraindications for noninvasive respiratory support (absolute contraindications are shown in bold)

1. Neurological
Inability to protect airways: compromised bulbar function, paralysis of the vocal chords, and altered level of consciousness
Severe psychomotor retardation
2. Craniofacial alterations:
Facial trauma or burns
Facial surgery
3. Gastrointestinal (GI)
Upper digestive tract surgery (esophageal or upper GI)
Profuse vomiting
Active digestive hemorrhaging
Obstruction of the intestinal tract
4. Respiratory
Severe acute respiratory failure
Undrained pneumothorax
Fixed obstruction of the upper airway
Upper airway surgery
Abundant heavy secretions
ARDS with PaO₂/FiO₂ <150
5. General
Severely compromised clinical state
Hemodynamic instability or shock
Postoperative arrhythmias following cardiac surgery
Congenital cardiopathies affecting pulmonary flow

Adapted with permission from original table in Medina et al. (2009)

- (h) *Pneumothorax*. Regardless of how it is delivered, positive pressure always has negative consequences in the untreated pneumothorax. However, NIV can be used in patients with drained pneumothorax.
- (i) *Recent gastrointestinal surgery*. Dehiscence of esophageal sutures has been described in patients who received NIV during the postoperative period. The entry of a large volume of air into the digestive tract with esophageal and/or gastric distension implies a risk during the immediate postoperative period. However, currently there are publications that demonstrate the efficacy and safety of NIV at low pressure in this setting.

Early detection and pre-assessment of these contraindications to NIV is crucial in order to avoid erroneous treatment of patients that should

instead be treated in another fashion, namely, with conventional mechanical ventilation. The presence of any relative contraindications should be weighed up together with the setting where it is going to be performed (ER, ward, PICU), the available logistics for the technique (ventilators, triggers, interfaces, fixation methods, monitoring), and the team that is going to manage the patient (training, experience).

17.2.6 Adjuvant Therapies: Helium–Oxygen (Principles and Clinical Experience) to Avoid Intubation

Helium, a naturally inert gas with a low molecular weight, when mixed with 21 % oxygen (the same concentration as in atmospheric air), produces a mixed gas one third the density of air. Its use in illness where obstruction in the airways is important is through reduced resistance to gaseous flow and, thus, in respiratory effort. Furthermore, heliox can improve gaseous exchange, improve alveolar ventilation, and also, through its high diffusion coefficient, increase the elimination of carbon dioxide. The cumulated published clinical evidence on pediatric use of heliox suggests its utility and efficacy for treatment of various conditions, including upper airway obstruction caused by diverse pathologies, as well as asthma and acute bronchiolitis.

There is very little evidence published on the combination of NIV and helium–oxygen. In our experience, nasal CPAP (nCPAP) is efficacious in severe bronchiolitis patients, not only in patients unresponsive to conventional treatment but also in those not responding sufficiently to treatment with heliox through a nonbreathing reservoir face mask. Furthermore, in bronchiolitis setting when nCPAP is used with heliox, it is significantly more efficacious than with air–oxygen. The response to heliox is seen rapidly within the first hour and is maintained during treatment, consistent with its mechanism of action. This first hour is important because, given the safety of heliox, we can widen the pool of patients treated, yet quickly detect nonresponders,

thereby minimizing ineffective treatment with prompt switching to other treatments.

There are no further data in the literature on the specific use of heliox and noninvasive ventilation in combination in infants with acute bronchiolitis. Based on current understanding of each of these treatments, the existing data in adults, and our initial experience in pediatric patients, we suggest that heliox–nCPAP is of clear additional benefit, even with synergy between the heliox and nCPAP. The nCPAP may contribute to decreased inspiratory muscle workload, prevent or relieve atelectasis, avoid airway collapse, and promote heliox distribution within the obstructed airways. Heliox can also reduce respiratory work, enhance carbon dioxide elimination, and increase expiratory flow at the same airway pressures compared with AO. This last effect may help improve passive expiratory pulmonary mechanics, reducing the risk of barotrauma from gas trapping and, thus, limiting the potential detrimental effects of nCPAP. Use of nCPAP may also reduce the FiO_2 needed in these children, further augmenting the actual helium concentration that may be delivered to the patient. On the other hand, it has been reported that heliox might cause hypoxia secondary to the development of atelectasis; this potential adverse effect—in case it exists—may be easily prevented with the concomitant use of nCPAP.

A literature review suggests that 25–60 % of infants with bronchiolitis admitted to a PICU may need intubation and ventilatory support. Although there may be influencing factors other than heliox and nCPAP treatment, such as PICU admission criteria, differences in RSV status, or disease stage or in intubation practices, between 1999 and 2006, only 1 (0.4 %) of 231 patients admitted to our unit with acute bronchiolitis and managed according to our protocol—centered on the use of heliox alone or in combination with NIV—has needed intubation and mechanical ventilation (95 % exact CI: 0.07–2.40 %).

Importantly, in none of the published studies and in our experience were there any adverse effects related to heliox, and the technique used was tolerated well in all of the patients. The inert nature of helium is responsible for the few

Table 17.7 Indications of noninvasive ventilation with helium–oxygen instead of air–oxygen

1. Children *already receiving heliox therapy*^a with inadequate oxygenation
Not meeting their oxygenation goals—requirements
Whose FiO_2 requirement is either >0.40 or increasing
2. Children *already receiving NIV* with inadequate ventilation
Ventilation level achieved is inadequate according to pH/ pCO_2
Require high or increasing pressure levels (PIP/IPAP)
Show insufficient improvement (or worsening) in dyspnea
Show insufficient improvement (or worsening) in clinical respiratory score
3. Children receiving NIV whose underlying pathology or illness *requires protective ventilatory strategy* (i.e., the lowest possible pressure/volume swings (amplitude/IPAP–EPAP) for achieving a target pH/ CO_2 level)

^aHeliox therapy defined as helium–oxygen mixture (60–80 % helium proportion) administered to a spontaneously breathing child through nonbreathing reservoir face-mask with adequate heliox flow (usually 10–15 lpm)

secondary effects not only in our patients but also in general clinical practice.

Despite our positive cumulated experience and the widespread use of noninvasive ventilation with heliox in our unit, no well-established indications of this technique in children exist. The author of this chapter has compiled a list of potential indications of heliox used with NIV for pediatric patients, based on the physical properties of heliox, published data from experimental reports, and clinical studies on adult patients, as well as his personal accumulated and published experience (see Sect. 2.3.1 for further details). According to this, the indications of noninvasive ventilation are summarized in Table 17.7 and mainly comprise two groups:

- (a) Children already receiving heliox therapy that are not achieving adequate levels of oxygenation
- (b) Children already on noninvasive ventilation with inadequate ventilation according to pH/ pCO_2 levels, dyspnea, or clinical score

One further indication, at least from the theoretical perspective, would be in those children

receiving NIV whose underlying pathology or illness requires protective ventilatory strategy (i.e., the lowest possible pressure–volume swing (amplitude/IPAP–EPAP) for achieving a target pH/CO₂ level). From the practical point of view, infants with severe unresponsive bronchiolitis and children with status asthmaticus are the most frequent clinical indications of noninvasive ventilation with heliox.

Future Perspectives

The interest in NIV is rapidly growing, but the evidence from the literature is still scarce, and it is coming in a slower fashion than the spread of its practical use. Despite the fact that the author of this chapter clearly favors the use of NIV in children, he acknowledges this imbalance between theory and practice that may lead to an overuse or inappropriate indication of NIV. This is particularly worrisome in units without experienced staff and/or well-developed protocols. Furthermore, any NIV protocol or algorithm should be frequently updated according to the newest evidence, as continued interest in NIV leads to greater technical expertise and clinical experience among professionals in the field.

There are obvious challenges for the pediatric NIV that need to be resolved, both from the technical and clinical research perspectives. We need to know if NIV actually prevents endotracheal intubation in children. Another unresolved issue relates to the cost of NIV and whether it is an efficient technique. Better NIV-specific ventilators (e.g., better triggers) and more specific pediatric material (e.g., interfaces, fixations) are required. Future studies will need to address unresolved questions surrounding the timing (starting point, duration), the early detection of nonresponders, the ideal settings, the preferred mode/interface.... Further studies comparing different NIV modes in different pediatric settings and analyzing factors to predict the

response to therapy should be warranted. More studies are needed to further assess the role of heliox in combination with NIV. We also need more trials to establish optimal pediatric guidelines for NIV use in children and precise information to select the adequate patients.

In the meanwhile, the horizon for the use of NIV is indeed bright, and no doubt ventilators and interfaces more and more appropriate for children will come. We hope we will be able to implement all these innovations according to well-designed and powerful clinical trials performed specifically in children.

Essentials to Remember

- Even though most of the supporting literature comes from adult studies, NIV in the pediatric patient is reasonably safe and efficacious.
- NIV should be seen as the “bridge” to recovery (or wellness) of our pediatric patient without the need of intubation and its related risks and inconveniences.
- A trial of NIV should be offered in time probably to all forms of acute respiratory failure.
- Children with a predominant hypercapnic failure (type II ARF) will be more prone to respond to NIV than those with hypoxemic ARF (type I ARF).
- The eagerness to avoid invasive ventilation should not delay endotracheal intubation in those cases where intubation really is necessary.
- The most important determining factor in pediatric NIV outcome probably is patient selection.
- Few absolute contraindications exist for noninvasive ventilation, severe neurological impairment, and significant hemodynamic instability being the more commonly accepted.

- Early detection and pre-assessment of NIV contraindications is crucial to avoid erroneous treatments.
- NIV with heliox is probably a safe and effective tool in infants with severe bronchiolitis although further studies are needed.

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The Pediatric Patient

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Educational Aims

- Recognize the most common mechanisms of respiratory failure in the newborn.
- Understand the major indications for mechanical ventilation in this age group.
- Assess the need for respiratory support and understand the risk benefits of invasive ventilation.
- Identify the different parameters utilized to determine the need for mechanical ventilation in the newborn.
- Know the most important targets used to adjust the ventilator settings in newborns.
- Understand the short- and long-term respiratory and neurological outcomes in infants who receive mechanical ventilation.
- Recognize some of the contraindications for mechanical ventilation in the newborn.

18.1 The Neonatal Patient

Eduardo Bancalari and Andreas Schulze

18.1.1 Introduction

The spectrum and severity of respiratory illness in the newly born has been changing over the past three decades with the introduction of antenatal steroids, improved management of the fetus during preterm labor and birth, and postnatal exogenous surfactant administration. Early pulmonary parenchymal failure requiring invasive ventilation occurs less frequently. Moderately preterm infants who received invasive mechanical ventilation in the past can often be managed nowadays with noninvasive respiratory support. There is, however, a “new generation” of surviving extremely small infants who depend on early initiation of invasive ventilation and who stay on the ventilator for extended periods of time with substantial risks for ventilator-induced lung

injury. Such infants often require invasive ventilation for reasons other than surfactant deficiency. These comprise, among others, respiratory pump failure and intermittent failure of the immature respiratory rhythm generator and control of breathing. Diverse invasive mechanical ventilation strategies and modalities have been developed to better address these problems; however, evidence of their effectiveness is still scarce. Therefore, the clinician's expertise in some of the basic invasive ventilation techniques and devices probably remains the key determinant of a successful application.

18.1.2 Major Indications for Invasive Assisted Ventilation

18.1.2.1 Critical Upper Airway Obstruction

Severe upper airway obstruction with or without other accompanying respiratory disorder may merit endotracheal intubation and assisted ventilation. An orally or nasally inserted artificial airway, i.e., endotracheal tube or laryngeal mask bypassing the stenosis, may already fully relieve the respiratory distress in some of these cases. It is sometimes impossible to place an artificial airway with the use of a laryngoscope. A thin flexible fibroscope is an alternative to visualize and enter the larynx and the trachea. It can subsequently serve as a guide wire to the endotracheal tube in such situation. Major obstruction can occur at all levels of the upper airway in the newborn. Bilateral choanal atresia is a rare condition with bony structures occluding the posterior nasal passage in about 90 % of cases. Other causes of obstruction at the supraglottic level include teratomas, anterior meningoencephaloceles, hemangiomas, hygromas, and variants of the Pierre Robin sequence or Treacher Collins syndromes where mandibular hypoplasia, cleft palate, and glossoptosis can be present to a varying degree. Some types of congenital intrinsic obstruction of the larynx and/or the trachea pre-

clude an endotracheal tube placement and may require a tracheostomy.

18.1.2.2 Respiratory Pump Failure

The respiratory pump consists of respiratory musculature and the thoracic cage. Both structures undergo major developmental changes during late fetal and early neonatal life. Immaturity of the respiratory pump makes several components of this system prone to failure. Failure will occur when the load exceeds pump strength. The load can be measured as work of breathing. Lung compliance and airway resistance are major determinants of this load. Inspiratory rib cage inward distortion is characteristic of the preterm newborn in whom the thoracic skeleton is floppy and intercostal muscle tone is low. Such chest wall distortion requires additional muscle work because the diaphragmatic volume displacement during inspiration does not fully translate into lung expansion and part of the diaphragmatic movement is wasted into rib cage distortion. Respiratory pump fatigue is defined as decreasing minute ventilation (tidal volume and/or respiratory rate) during continued respiratory load. Failure can occur at three different sides: central fatigue (reduced phrenic nerve output), neuromuscular transmission failure (decreasing EMG activity at normal or increased phrenic nerve activity), and muscle contractile failure (decreased diaphragmatic pressure output despite increased EMG and phrenic nerve activity). Several indexes (tension-time index, maximum inspiratory diaphragmatic force, and others) have been proposed as means to recognize impending respiratory muscle failure and the need for assisted ventilation in the newborn. Such measures could also be helpful for predicting failure of weaning from assisted ventilation and extubation. However, evidence of the clinical utility of these indexes is still pending. Clinical judgement by an experienced neonatologist therefore currently still appears the most valuable tool to recognize impending fatigue as a reason to initiate assisted ventilation.

18.1.2.3 Central Control of Breathing Failure

The control of breathing system involves neuronal networks in the brainstem with populations of cells that exhibit rhythmic intrinsic bursting activity. They are but one component of a neural feedback with the overall objective to maintain blood gas homeostasis. Peripheral oxygen sensors, central carbon dioxide sensors, and intrapulmonary mechanoreceptors feed signals into the circuit. Commonly, this feedback provides for an overall stable breathing pattern. The majority of this system's components undergo major maturational changes in the fetus. Respiratory instability in the immature infant may present with a wide range of breathing patterns such as periodic breathing, hypopnea, and recurrent apnea which may be unresponsive to medication and require mechanical ventilatory assist. The newborn is largely unable to mount sustained hyperventilation during hypoxia which also contributes to a propensity of the central control to fail.

18.1.2.4 Intrapulmonary Conditions Causing Respiratory Gas Exchange Failure

In the newborn, pulmonary parenchymal disease is often caused by several combined pathophysiological conditions that ultimately may lead to respiratory gas exchange failure. Among others, these are structural immaturity, surfactant deficiency, shunts across a patent ductus arteriosus, inflammatory changes and pneumonia, intrapulmonary hemorrhage, and malformations.

There are three major causes of arterial hypoxemia:

- Right-to-left shunt, either intrapulmonary (mainly caused by atelectasis) or extrapulmonary (at the ductal or atrial level)
- Ventilation-to-perfusion mismatch (particularly in infants with chronic lung disease)
- Hypoventilation
- Diffusion impairment

These conditions typically respond with an improvement in oxygenation when the fraction

of inspired oxygen is increased. This, however, does not occur if there is a right-to-left shunt of more than about 30 % of cardiac output. Diffusion impairment is regarded to be a very uncommon cause of hypoxemia in the newborn.

A critical impairment of pulmonary carbon dioxide removal is usually caused by alveolar hypoventilation but ventilation-to-perfusion mismatch can also contribute to the problem.

18.1.3 Assessment of Need for Mechanical Ventilation

The decision to initiate invasive mechanical ventilation in the newborn is an important step because of the short- and long-term complications associated with this mode of therapy. This is especially relevant in the smaller preterm infants. There is no standard approach and considerable variation exists between different centers in the criterion to initiate mechanical ventilation. This decision must take into consideration the gestational age of the infant, the degree of respiratory failure, and the disease process that is producing the respiratory failure together with the alternatives available to support the infant's respiratory function. It is also important to take into consideration the experience of the team and the expected outcome of infants exposed to mechanical ventilation in each institution. While in units with vast experience and good outcomes, ventilation may be used more liberally; in units with limited experience, safer alternatives should be considered before embarking in invasive ventilation.

The indication of invasive ventilation is usually based on the clinical assessment of the infant combined with the evaluation of arterial blood gas levels. In the smaller infants ventilation is often begun in the delivery room because of respiratory depression and bradycardia or because of the need to administer surfactant. Subsequently many preterm infants are ventilated because of recurrent episodes of apnea and hypoxemia that require mask ventilation to

recover. In other situations ventilation is initiated when levels of $P_a\text{CO}_2$ rise rapidly. Although there is no specific level of $P_a\text{CO}_2$, most clinicians consider mechanical ventilation when levels rise acutely above 55–65 mmHg and the pH is below 7.25–7.20.

The other parameter considered for initiation of ventilation is hypoxemia that does not improve with continuous positive airway pressure. Again, there are no set levels of $P_a\text{O}_2$ or FiO_2 to start ventilation, but in preterm infants with hyaline membrane disease (HMD), the decision to insert an endotracheal tube and initiate mechanical ventilation is frequently linked to the decision to administer exogenous surfactant. The indication varies between institutions, but there is good evidence that early administration of surfactant results in better outcome and therefore in an infant with HMD surfactant is usually given when the inspired oxygen concentration required to keep acceptable $P_a\text{O}_2$ or oxygen saturation levels increases above 30–40 %. Ventilation may be started earlier if the infant has hypercapnia or clinical signs of significant distress and impending failure. In many centers surfactant is given as prophylaxis to all infants below a certain gestational age, usually 26–28 weeks, and if the infant has good respiratory effort is then extubated to nasal CPAP.

In full-term infants, the indication for mechanical ventilation can be more conservative since these infants have better capacity to cope with increased work of breathing. It also varies depending on the underlying cause of the respiratory failure. For example, in an infant with respiratory failure due to a congenital diaphragmatic hernia, ventilation is usually started immediately after birth, while in an infant with a congenital pneumonia or meconium aspiration, a more conservative approach can be taken and ventilation is usually not started until there is evidence of rising $P_a\text{CO}_2$ and hypoxemia, requiring increasing inspired oxygen concentrations up to 40–60 %. Once again, the clinical evaluation of the infant is important in deciding whether invasive ventilation should be started or not.

It is important to note that the use of positive pressure ventilation seldom results in improved lung function and in fact frequently can produce further deterioration due to the negative effects of

high inspired oxygen concentrations, pulmonary infection, and excessive airway pressure and over-distention of the lung. The effectiveness of mechanical ventilation is primarily due to the support of the infant's failing respiratory pump by the intermittent positive pressure generated by the ventilator and reduction in the work of breathing. An exception to this is the infant with HMD where the positive airway pressure can produce recruitment of distal air spaces with improvement in ventilation perfusion matching and gas exchange.

18.1.4 Ventilation Targets

18.1.4.1 Oxygen

Because of the potential side effects of oxygen therapy, the oxygenation target is extremely important especially in the small preterm infant. Despite this, the available information on the optimal oxygen targets is limited. Although the negative effects of extreme hyperoxia and hypoxia are well established, there is little data on what the range for $P_a\text{O}_2$ or oxygen saturation should be for infants of different gestational or postnatal ages. In the small preterm infant, there is evidence that prolonged exposure to $P_a\text{O}_2$ over 70 mmHg is associated with increased risk of retinopathy of prematurity (ROP) (Bancalari et al. 1987; Flynn et al. 1992). The same has been shown for exposure to oxygen saturations over 95 % (Tin et al. 2001). For this reason it is recommended to keep $P_a\text{O}_2$ and saturations below these levels. This does not only reduce the risk of ROP, but limiting the amount of oxygen in the inspired gas can also reduce pulmonary damage and the incidence of BPD (Askie et al. 2003; Phelps et al. 2000). While this is less critical in the full-term infant, there is compelling evidence that in these infants, the exposure to excessive oxygen concentrations can also be associated with oxidative damage (Vento et al. 2003). Less clear is what the lower limit of oxygenation should be, so until evidence from ongoing clinical trials becomes available, it is recommended to keep the lower levels of $P_a\text{O}_2$ above 50 mmHg and pulse oximetry saturations above 85–88 %. Exceptions to these limits are infants with certain congenital heart diseases where lower values may be accept-

able or even desirable as in cases of single-ventricle physiology where low alveolar PO_2 may be used as a way of limiting pulmonary blood flow and preserving systemic blood flow.

18.1.4.2 Carbon Dioxide, pH

In general terms, the aim during mechanical ventilation is to normalize ventilation and gas exchange, and therefore the clinician tries to keep P_aCO_2 between 40 and 50 mmHg. While this is easily achievable in infants with relatively normal lung function, it becomes more difficult as the alteration in lung function is more severe and this requires high ventilator settings. In order to avoid these potentially damaging aggressive settings, the option of allowing higher P_aCO_2 levels has been used both in adults and infants as long as the pH is >7.25 – 7.30 . This strategy has been labeled “permissive hypercapnia.” This modality has also been investigated in preterm infants, and although it was suggested that it may shorten the duration of ventilation, there was no clear evidence that led to an improved long-term pulmonary outcome (Carlo et al. 2002; Mariani et al. 1999). In fact one of the most recent trials suggested that infants with higher P_aCO_2 could have higher mortality and worse neurological outcomes (Thome et al. 2006). These results have discouraged clinicians to use high P_aCO_2 levels in small preterm infants. However, in order to wean infants with chronic lung disease, it is necessary to tolerate higher P_aCO_2 levels, sometimes in the 70s or 80s before and immediately after extubation. These patients frequently have a compensatory metabolic alkalosis that results in a relatively normal pH.

Some years ago, many infants, specifically those with pulmonary hypertension, were managed with hyperventilation and low P_aCO_2 levels. This approach has been abandoned because it produces cerebral vasoconstriction and may result in worse neurological outcome (O’Shea and Dammann 2000). Because to achieve hyperventilation it is necessary to use aggressive ventilator settings, it is also associated with increased lung damage and higher incidence of BPD (Kraybill et al. 1989). For these reasons hyperventilation has been abandoned and should be avoided in the newborn.

18.1.4.3 Airway Pressures, Lung Volume

Ideally the level of positive end-expiratory pressure (PEEP) should be based on measurements of lung volume. While there are methods to measure FRC in small infants, these measurements are not done in routine clinical practice, and therefore the selection of PEEP level is based on the degree of lung disease, arterial oxygenation, and radiographic appearance of the lungs. Although there is no clear data in the neonate, most clinicians have adopted levels of PEEP that usually range from 3 to 8 cm H_2O . The higher levels are used in infants with more severe lung disease where these pressures are necessary to stabilize the distal airways and preserve FRC and oxygenation. The concerns with higher levels of PEEP are overdistention of the lungs with the risk of alveolar rupture, and decrease in venous return and cardiac output with an increase in pulmonary vascular resistance. Excessive PEEP levels can also result in lower lung compliance and hypoventilation (Alegria et al. 2006; Dimitriou et al. 1999). Work in experimental animals has also shown that high levels of PEEP can increase capillary permeability and increase neutrophil migration into the lung (Naik et al. 2001).

The selection of peak inspiratory pressure (PIP) is simpler now that most ventilators allow the measurement of flow and tidal volume. In general terms one selects the PIP that results in a tidal volume of 3–5 ml/kg body weight. The level of PIP is also adjusted depending on P_aO_2 and P_aCO_2 levels. Presently most infants are ventilated with patient-triggered ventilators, and most of the tidal volume is generated by the infant while the PIP is used only to support their effort and achieve the desired ventilation and oxygenation. With this strategy most infants can be ventilated with PIP levels below 20 cm H_2O , and when the lung disease is less severe, pressures of 6–12 cm H_2O above PEEP are usually sufficient to maintain ventilation. The level of pressure required depends on the severity of the derangement in lung compliance and resistance and the spontaneous effort that the infant is capable of generating at each stage of their disease process. Because higher airway pressures are associated with increased risk of acute and long-term

lung damage, the PIP target should always be the lowest level required to keep adequate tidal volumes and minute ventilation.

18.1.5 Short- and Long-Term Outcome

The acute complications and survival of infants who receive mechanical ventilation are closely related to the criteria and indications for initiating ventilatory support, to the underlying condition of the infant, and to the experience and skills of the personnel providing this therapy. The more liberal the indication for IPPV, the better the results should be. In preterm infants the gestational age and associated conditions are the most important determinants of outcome.

While the survival of extreme premature infants has increased in the last two decades, the incidence of complications such as BPD has not changed or may even be increasing. This should be expected because the smallest new survivors are at increased risk for the major complications associated with extreme prematurity (St John and Carlo 2003). This may also be in part due to the less frequent use of postnatal steroids since the late 1990s.

In a retrospective analysis of prospectively collected data from the NICHD Neonatal Research Network, the overall survival of 4,752 ventilated infants with birth weight of 501–1,000 g was 74 % (Walsh et al. 2005). The median duration of ventilation was 18 days (23 days in survivors and 6 in non-survivors). Twenty-five percent of the infants remained on mechanical ventilation by 36 days and 7 % were ventilated for more than 60 days. Thirty-nine percent of the surviving infants developed chronic lung disease.

The incidence of pneumothorax associated with mechanical ventilation has decreased from 10 to 15 % in the pre-surfactant era to around 5 % after the introduction of postnatal surfactant replacement. In contrast, the incidence of pulmonary hemorrhage has remained relatively constant or even increased in the smallest infants in

whom the incidence can be as high as 10–15 % (St John and Carlo 2003). This complication has been associated with the use of exogenous surfactant and with the persistence of the ductus arteriosus and increased pulmonary blood flow.

Ventilator-associated pneumonia is a common complication of mechanical ventilation in any age group, and it is likely to occur even more frequently in the immunocompromised premature infant. Unfortunately, it is not commonly diagnosed in this population because of the lack of specific criteria and the difficulty in differentiating a pneumonia from other acute and chronic pulmonary pathologies that occur frequently in infants requiring prolonged mechanical ventilation (Cordero et al. 2002).

The long-term outcome of infants treated with IPPV is more related to the patient characteristics than to the use of mechanical ventilation. Bronchopulmonary dysplasia is the most common long-term pulmonary sequela associated with mechanical ventilation, and its incidence and severity are mainly associated with the gestational age and severity of the initial respiratory failure (See Chronic Respiratory Failure in Neonates).

There is evidence that even in premature infants who do not develop BPD, there is an increased risk of lower respiratory tract infections early in life, and there are pulmonary function abnormalities reflecting obstructive airway disease that may persist later in life (Kitchen et al. 1992). It is not clear whether these abnormalities are mainly related to the premature birth or to the use of mechanical ventilation (Chan et al. 1989). There is also a reported increased incidence of asthma in preterm survivors when compared to controls (Halvorsen et al. 2004). Infants with BPD may have severe reduction in airflow later in life but this airway obstruction varied little with the severity of BPD and was also present in ventilated infants who did not develop BPD (Doyle 2006; Doyle et al. 2006).

Mechanical ventilation has also been associated with impaired neurodevelopmental outcome. Thirty-one percent of 2,755 infants 500–1,000 g exposed to mechanical ventilation

and tested for neurodevelopmental outcome had an MDI < 70, and 22 % had a PDI < 70. Nine percent of the tested infants had moderate to severe cerebral palsy. These impairments were more common in infants who remained on mechanical ventilation past 28 days. Additional risk factors for poor neurodevelopmental outcome were non-white race, male gender, grade III–IV IVH, and low maternal education level (Walsh et al. 2005). It is not clear whether in infants with chronic lung disease the poor development outcome is related to the respiratory disease or to the multiple factors that predispose these infants to BPD (Laughon et al. 2009).

Infants with BPD are at a significantly higher risk for developing cerebral palsy (Short et al. 2003; Skidmore et al. 1990; Vohr et al. 1991, 2005). This may be in part due to the use of post-natal steroids, a therapy that is known to be correlated with higher incidence of CP (O'Shea et al. 1999; Shinwell et al. 2000; Yeh et al. 1998). Infants with BPD also have lower developmental scores and poorer school performance than survivors without chronic lung disease (Short et al. 2003; Gray et al. 2004; Hughes et al. 1999; O'Shea et al. 1996; Robertson et al. 1992; Taylor et al. 1998).

18.1.6 Contraindications of Invasive Mechanical Ventilation

Mechanical ventilation is usually considered a life-saving therapy that is instituted in infants with severe respiratory failure, most of whom would not survive without this therapy. Therefore, there are no specific contraindications to initiate mechanical ventilation when this is properly indicated. There are some situations when the indication may be questionable because of the poor expected outcome such as in infants at the border of viability, after severe perinatal asphyxia, or with life-threatening congenital malformations. A similar situation may occur when the risks of invasive ventilation are so high that they outweigh the possible benefits of this therapy.

Essentials to Remember

- The indication of mechanical ventilation should be determined by the risk benefit analysis in each infant.
- The effectiveness and safety of mechanical ventilation are related to the expertise of the clinical team.
- Mechanical ventilation supplements or replaces the respiratory pump but rarely improves lung function. On the contrary it can produce severe lung injury.
- The levels of pressures used during IPPV are determined by the severity of the lung disease and are adjusted to generate adequate tidal volumes and oxygenation.
- The short- and long-term outcomes in infants who receive mechanical ventilation are determined by the gestational age and the underlying condition of the infants and the experience and expertise of the clinical team.

18.2 The Pediatric Patient

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Educational Aims

- Understand the primary indications for the initiation of invasive ventilation.
- Review the relationship between a child's underlying physiologic state and disease process as they relate to the need for mechanical ventilation.
- Review the causes of impaired gas exchange.
- Understand the impact of neuromuscular weakness on a patient's respiratory status.
- Review the Glasgow Coma Scale score.
- Recognize that neurologic dysfunction is an important indication for airway protection.

- Understand the cardiopulmonary interactions created by positive pressure ventilation.
- Learn the importance of a global assessment in the evaluation of the need for invasive ventilation.
- Understand the consequences and potential complications related to invasive ventilation.

18.2.1 Introduction

Acute respiratory failure remains the leading diagnosis for children admitted to intensive care units (ICUs) and accounts for a significant burden of mortality and morbidity in the pediatric population. Invasive mechanical ventilation, or the use of an advanced airway to provide life support, is paramount in the care of children with lung injury as well as many other disease processes. Furthermore, duration of mechanical ventilation is a major determinant of both ICU cost and length of stay (Cheifetz 2003).

Optimizing care of ventilated children provides a host of challenges. A crucial problematic issue is the management of patients over a wide range of sizes and developmental stages. Not only are pediatric airways of different diameters and lengths, but they also change dramatically as they develop: the tongue becomes relatively smaller, the larynx becomes less anterior and moves caudad, and the subglottic space becomes less cone shaped and more cylindrical (Cote et al. 2001). As children grow, they have widely varying baseline respiratory rates, tidal volumes, and metabolic demands.

As patients change in size, the equipment needed for mechanical ventilation must adapt. Ventilators must be able to effectively deliver a wide range of tidal volumes while being sufficiently sensitive to appropriately monitor small flow rates and pressure changes. The use of equipment that is not designed for pediatric patients may lead to the delivery of unsafe tidal

volumes and/or pressures or the inability to maintain appropriate ventilation targets.

Finally, children are affected by different disease processes than either adults or premature infants, yet few studies exist that evaluate ventilation strategies for the pediatric population. Much of accepted clinical practice has been derived from studies in adults, neonates, or animals. This often forces the pediatric provider to adopt ventilatory strategies which were tested on a population with different disease states and potentially dissimilar responses to treatment.

Prior to initiating invasive mechanical ventilation in the pediatric patient, the bedside clinician must address each of these questions:

1. Do I have the support of someone who is competent in the management of pediatric airways?
2. Do I have the proper equipment not only to secure the airway but to ventilate this child in a safe manner?
3. Do I have the knowledge and experience to appropriately ventilate this patient's specific disease process(es)?

Children requiring mechanical ventilation have benefited greatly from advances in both ventilation techniques and ventilator technology. When facing a critically ill child, it is imperative for front-line, noncritical care medical providers to use resources available to them, such as on-call anesthesiologists, intensivists, and referral to tertiary care centers.

18.2.2 Primary Indications for Assisted Ventilation

The need for invasive mechanical ventilation may arise from a wide range of disease processes. In children, specifically, the impact of any given disease depends not only on the pathologic process but also on the physiologic state of the child. Differing degrees of physiologic reserve exist as children progress through the normal development process, and significant variability exists between the response to illness and injury between a young infant and an adult-sized adolescent. An understanding of this normal physiologic development is crucial in the setting of

critical illness when determinations are being made regarding the potential need for invasive mechanical ventilation. For example, a viral respiratory infection that may be only a minor annoyance in an otherwise healthy adult can have devastating consequences and complications in a young infant. There are a range of circumstances in which substantial variability exists in both presentation and progression of disease depending on the age and physiologic state of the child.

A wide spectrum of clinical situations may require invasive mechanical ventilation in children, including both primary respiratory failure of various etiologies and organ dysfunction not directly related to the respiratory system. Invasive ventilation may be necessary for airway protection in the setting of neurologic dysfunction, including trauma, seizures, neuromuscular weakness, and/or other causes of altered mental status. Similarly, dysfunction of the cardiovascular system, secondary to congenital disease or an acute acquired process (e.g., myocarditis), may also necessitate mechanical ventilation to decrease metabolic demands. It is important to complete a thorough global assessment, including a comprehensive history and physical examination that includes all major organ systems, as one works to determine when invasive mechanical ventilation is indicated. In this section, we will examine four major categories of illness that may require invasive ventilation: unstable airways, impaired gas exchange, respiratory muscle insufficiency, and need to reduce mechanical ventilatory load. While this list is not all-inclusive, it does provide the majority of reasons for which pediatric patients require assisted ventilation.

18.2.2.1 Unstable Airways

18.2.2.1.1 Anatomic Airway Integrity

Airway integrity can be challenged by either anatomical or neurological insults. From an anatomical view, the upper airway includes the space from the lips and nares to the subglottic region, including the tongue, teeth, nasal turbinates/septum, adenoids, tonsils, pharynx, and larynx. Obstruction to airflow may occur at any of these levels, necessitating intervention (Table 18.1).

Table 18.1 Causes of upper airway obstruction

Infectious/inflammatory
Tracheobronchitis (croup)
Bacterial tracheitis
Epiglottitis
Peritonsillar abscess
Retropharyngeal abscess
Anaphylaxis
Angioedema
Trauma
Facial or neck trauma
Facial or inhalational burns
Foreign body
Congenital/syndromic
Macroglossia (trisomy 21, Beckwith-Wiedemann syndrome, etc.)
Micrognathia (Pierre Robin sequence, etc.)
Midface hypoplasia (Crouzon's Syndrome, etc.)
Tracheo-laryngomalacia
Subglottic stenosis or obstruction
Vocal cord paralysis or malformations
Anatomic
Cystic hygroma
Branchial cleft cyst
Thyroglossal duct cyst
Vascular ring
Intrathoracic mass or tumor

Clinically, impending respiratory failure may present as a marked increase in the patient's work of breathing or as inadequate gas exchange (usually hypoxia).

In the pediatric population, the most common causes of upper airway obstruction are infectious, including tracheobronchitis (croup), bacterial tracheitis, and retropharyngeal abscess (Leung et al. 2004; Skolnik 1989). However, only a small percentage of children with these diseases will progress to the need for an advanced airway. Epiglottitis can also lead to an extremely tenuous airway but fortunately has been almost eliminated in the developed world following universal administration of the haemophilus influenzae type b (Hib) vaccine (Leung et al. 2004).

Congenital airway malformations such as micrognathia, macroglossia, and tracheo-laryngomalacia are also significant causes of upper airway obstruction, particularly in neonates

and infants (Lahiri 1996; Lerner and Perez Fontan 1998). A variety of genetic and metabolic syndromes are associated with upper airway obstruction, including trisomy 21, Crouzon's Syndrome, Pierre Robin sequence, mucopolysaccharidoses, and some glycogen storage disorders. The majority of cases of tracheo-laryngomalacia will not require invasive mechanical ventilation, as malacia often improves as the child's airway grows and muscle tone improves. However, with severe fixed upper airway obstruction, providing a secure airway and mechanical ventilation may be necessary to bridge patients to surgical correction or amelioration (i.e., tracheostomy).

Trauma to the oral cavity, mandible, or maxilla may also create an unstable airway that requires early, or even immediate, intervention. Similarly, inhalational burns and facial burns may have rapid, massive swelling that may compromise a patient's airway. It is generally recommended that these burn patients be intubated on presentation to protect the airway (Cochran 2009). Similarly, it is generally recommended to establish an advanced airway early in the course of anaphylaxis, angioedema, or any other process that involves significant (or potentially significant) swelling of the airway.

Patients with epiglottitis, congenital airway malformations, severe facial trauma, and airway or facial burns must be considered high-risk airways. Intubation should be undertaken by providers experienced with difficult airways and often with the support from fiber-optic technology. Even with supportive technology, it may not be possible to visualize such an airway, and advanced techniques may be required to secure the airway, including laryngeal mask airway (LMA), blind intubation, or emergency cricothyrotomy or tracheostomy.

While tracheal tubes stent the airway from the lips to the subglottic space, mechanical ventilation may also be necessary for some anatomical problems of the lower airways or thorax. Flail chest represents an injury to the chest wall that requires positive pressure ventilation to inflate the ipsilateral lung. Congenital diaphragmatic hernia requires early intubation to minimize air

accumulation in the intrathoracic stomach and intestinal tract. Finally, severe bronchomalacia may require positive pressure to maintain patent lower airways.

Another important unstable airway situation is the patient with a large anterior mediastinal mass. These patients may require intubation for respiratory distress secondary to tracheal and/or bronchial compression, or electively for patient transport or diagnostic procedures. However, management of the airway in the patient with an anterior mediastinal mass should be undertaken with extreme care. Airway compression may acutely worsen when the patient is placed in the supine position. In addition, administration of even small amounts of sedation/analgesia often relaxes native airway tone and may precipitate acute (and sometime irreversible) cardiopulmonary collapse. For these reasons, patients with anterior mediastinal masses should be intubated with extreme caution, and potential considerations include performing this procedure in the operating room, preserving spontaneous breathing, using fiber-optic techniques, and maintaining a sitting position.

18.2.2.1.2 Neurologic Dysfunction

Neurologic dysfunction secondary to trauma, seizures, metabolic disease, or toxic ingestion may lead to loss of airway protective reflexes. Invasive mechanical ventilation is necessary in these circumstances to not only maintain gas exchange but to also prevent aspiration and allow for necessary diagnostic and therapeutic interventions.

Depending on the age of the patient, assessment of neurologic dysfunction in pediatric patients and determination of the optimal timing of intubation and initiation of mechanical ventilation may be quite challenging. Attention should be paid not only to airway reflexes but also to mental status and global neuromuscular strength and tone. As neurologic dysfunction progresses, it is preferable to address potential airway concerns early, before respiratory deterioration occurs. This proactive approach allows for a thorough pre-intubation assessment and the carefully controlled management and establishment of a secure airway.

18.2.2.1.2.1 Seizures

In the setting of seizures and status epilepticus, respiratory insufficiency and inadequate airway protection may be secondary to the convulsive activity and/or treatment of the seizure(s). Regardless of the etiology, as many as 30 % of patients with refractory status epilepticus require intubation and mechanical ventilation, making it important to plan for this possibility as seizure treatment is initiated (Lewena et al. 2009). One special consideration in the setting of seizures includes the impact of neuromuscular blockade on monitoring for further seizure activity. In this setting, intubation without neuromuscular blockade or the use of a short-acting neuromuscular blocker (e.g., rocuronium) should be considered so as to avoid masking further/ongoing seizure activity. If more prolonged neuromuscular blockade is necessary in these circumstances, electroencephalographic monitoring should be initiated.

18.2.2.1.2.2 Traumatic Brain Injury

Traumatic brain injury (TBI) is another situation in which mechanical ventilation may be required for airway management. The Glasgow Coma Scale (GCS) score is most commonly used in the setting of traumatic brain injury as an objective measure of neurologic dysfunction that can be followed over time (Table 18.2). This score ranges from 3 to 15, and usually, a GCS of 8 or less indicates that a patient is unlikely to be able to safely maintain his/her airway. When deciding on intubation using the GCS, the trajectory of change is an essential component. A patient who deteriorates from a GCS of 14–10 may be in need of airway protection; while the patient who is improving from a GCS of 6–8 may not require invasive ventilation as long as close, continuous monitoring is provided. Similarly, the GCS score may be less predictive of overall status in a patient who is postictal or developmentally delayed. The decision of when to establish an advanced airway must be made with consideration of the individual patient’s baseline condition, mechanism of injury, and anticipated clinical trajectory.

Table 18.2 Glasgow Coma Scale (GCS) score

Eye opening	4 – Spontaneous eye opening 3 – Eyes open to command 2 – Eyes open to painful stimulation 1 – No eye opening
Verbal response	5 – Clear and understandable speech 4 – Inappropriate but comprehensible speech 3 – Unintelligible speech 2 – Makes sounds in response to painful stimulation 1 – No speaking
Motor response	6 – Follows commands 5 – Localizes painful stimulation 4 – Withdraws to painful stimulation without localization 3 – Flexion movements (decorticate posturing) 2 – Extension movements (decerebrate posturing) 1 – No movement

While declining mental status is one important indication for intubation in the setting of neurologic dysfunction, a secure airway may also be necessary prior to diagnostic radiographic studies (e.g., computed axial tomography or magnetic resonance imaging scans) or therapeutic interventions (e.g., mild hyperventilation). Important considerations in the initiation of mechanical ventilation in the setting of traumatic brain injury are the effects on both intracranial and intrathoracic pressure. These factors can have significant implications not only on pharmacologic induction and the actual intubation procedure but also on the management of the patient after the airway has been secured.

18.2.2.2 Impaired Gas Exchange

The principal functions of the respiratory system are absorption of oxygen, needed for cellular energy metabolism via oxidative phosphorylation, and the removal of carbon dioxide, a by-product of the same metabolism reaction. At baseline, healthy individuals have a large respiratory reserve that will allow them to maintain adequate ventilation over a wide range of physiologic states and lung diseases. However, severe cases

of lung injury or airflow disturbance may lead to insufficient gas exchange and subsequent hypoxia and/or hypercarbia.

18.2.2.2.1 Hypoxia

Hypoxic respiratory failure secondary to inadequate gas exchange is one of the most common indications for mechanical ventilation in the ICU setting (Randolph 2009). Patients with hypoxia generally present with respiratory distress, tachypnea, increased work of breathing, and an increased A-a gradient (difference between alveolar (A) and arterial (a) oxygen tension). This systemic hypoxia leads to inadequate oxygen delivery to the various tissues and organs throughout the body, metabolic acidosis, and lactic acidosis. Invasive mechanical ventilation will improve hypoxia by increasing the mean airway pressure (P_{AW}), which is primarily accomplished by increased positive end-expiratory pressure (PEEP). Improved tissue oxygenation may also result from a subsequent reduction of oxygen consumption due to the initiation of mechanical ventilation.

There are a number of potential etiologies for hypoxia, which may involve any component of the respiratory system from the oropharynx through the alveolar-capillary membrane (Table 18.3). The end result of hypoxemic respiratory failure is similar, irrespective of the underlying cause, but these etiologies have important therapeutic implications.

Hypoxia secondary to upper airway obstruction presents with stridor, which may be inspiratory, expiratory, or biphasic in nature, depending on the location of the obstruction. Obstruction may be mechanical, infectious, and/or inflammatory, and the institution of invasive ventilation should be performed with caution given the potential difficulty bypassing the obstructed portion of the tracheobronchial tree. If not reversed, as obstruction worsens, air entry becomes progressively compromised. This progression can lead to hypoventilation, cyanosis, mental status change, and potentially complete cardiovascular collapse.

Parenchymal lung disease is another important cause of hypoxic respiratory failure and

Table 18.3 Causes of hypoxia

Airway obstruction
Hypoventilation
Ventilation/perfusion (V/Q) mismatch
Hemoglobinopathies
Abnormal pulmonary diffusion
Intracardiac right to left shunt

Table 18.4 Etiologies of parenchymal lung disease

Acute respiratory distress syndrome
Anaphylaxis
Inhalational injury
Near drowning
Pancreatitis
Pulmonary infection
Sepsis/severe inflammatory response syndrome (SIRS)
Transfusion-related lung injury (TRALI)
Trauma
Aspiration pneumonitis
Connective tissue disease
Inhalational injury
Pleural effusion/empyema
Pneumonia
Atypical
Bacterial
Fungal
Mycobacterial
Parasitic
Pulmonary hemorrhage
Pulmonary fibrosis
Vasculitis

may be secondary to a range of both infectious and noninfectious causes (Table 18.4). Parenchymal lung disease often presents with acute hypoxia along with the typical signs of respiratory distress and impending respiratory failure. Pulmonary examination reveals adventitious sounds either diffusely or in a focal area. As with airway obstruction, therapy for parenchymal disease should not only involve the use of invasive ventilation to correct abnormalities in gas exchange but should also focus on addressing the underlying cause of the impairment.

Similarly, ventilation/perfusion (V/Q) mismatch may be present in the setting of acute respiratory distress syndrome (ARDS) or in the presence of pulmonary, air, or fat emboli. Intrapulmonary and intracardiac right-to-left shunts also cause functional V/Q mismatch resulting in hypoxia resistant to oxygen therapy. An understanding of the physiologic relationship between ventilation and perfusion in the lung and how it changes in the setting of mechanical ventilation is crucial as positive pressure ventilation is initiated in these patients.

18.2.2.2.2 Hypercarbia

Hypercarbia primarily presents secondary to inadequate minute ventilation from inadequate tidal volumes or decreased respiratory rate. Lung injury causes hypercarbia through small inhaled tidal volumes due to markedly reduced lung compliance and by V/Q mismatch from increased physiologic dead space. In other patients, inadequate ventilation may also present secondary to muscle weakness, altered mental status, toxin exposure, or iatrogenic oversedation. If a reversible cause is not identified, these patients will generally benefit from provider-controlled ventilation. Mechanical ventilation allows the bedside provider to supply increased tidal volumes and a controlled rate, leading to increased minute ventilation. Such interventions should lead to enhanced carbon dioxide removal.

18.2.2.2.3 Lower Airway Obstruction

Respiratory distress secondary to lower airway obstructive disease similarly presents with hypercarbia, tachypnea, and increased work of breathing. Instead of audible stridor, wheezing and a prolonged expiratory phase are present on physical examination. As lower airway obstruction progresses, dynamic hyperinflation and air trapping worsen, leading to further prolongation of the expiratory phase and, in the extreme, a “silent chest.” A silent chest is an ominous situation in which gas exchange becomes severely compromised, and breath sounds become inaudible on physical examination. Inflammation of the lower airways is the most common cause of lower air-

way obstruction, in the form of asthma or bronchiolitis. Chronic lung disease of prematurity (i.e., bronchopulmonary dysplasia) is another important cause. Of note, a bronchial inhaled foreign body may lead to air trapping through a ball-valve mechanism, but because of its focality, this rarely causes significant retention of carbon dioxide.

The initiation of invasive ventilation in the setting of lower airway obstruction may be necessary but does carry substantial risk. In the setting of status asthmaticus and severe bronchospasm, children generate significant negative inspiratory pressure to maintain adequate ventilation. This extreme respiratory effort and air trapping leads to overexpansion and hyperinflation of the lungs and a significant increase in mean airway pressure. This may impair venous return to the right ventricle and reduce global cardiac output (Bohn and Kissoon 2001; Bove and Santamore 1981). The transition to positive pressure ventilation with potential worsening of air trapping and subsequent further compromise of systemic venous return may precipitate complete cardiovascular collapse.

In the patient with significant lower airway obstruction, the lungs approach a maximally hyperinflated volume. Pulsus paradoxus occurs when cardiac output is compromised to the point that systolic blood pressure drops by more than 10 mmHg with each inspiration as venous return is impeded. This hemodynamic change is an important indicator of the severity of lower airway disease, and in this situation, the initiation of positive pressure ventilation is considered particularly high risk.

In addition, the transition to positive pressure ventilation in the setting of asthma and severe bronchospasm creates a substantial risk for air leak and pneumothorax. Given the fact that lower airway obstruction is primarily a disease of ventilation and exhalation, forcing air into the lungs using positive pressure often further exacerbates dynamic hyperinflation and air trapping. Extreme caution, anticipation of consequences, and meticulous monitoring are all necessary in this situation to minimize the potential risks of positive pressure ventilation.

Due to these risks, intubation in the setting of status asthmaticus should be undertaken only in extreme circumstances. There are no clear indications for initiation of mechanical ventilatory support in asthmatics, but it may be necessary in the setting of impending respiratory failure as evidenced by alteration of mental status, declining respiratory rate in the setting of worsening gas exchange, progressive and refractory metabolic acidosis, or extreme exhaustion (e.g., “tiring out”) (Bohn and Kissoon 2001). As mechanical ventilation is initiated, careful attention should be paid to the patient’s intravascular volume status and augmentation of preload, along with the necessary titration of ventilatory support to optimize expiration and ventilation and, thus, minimize air trapping.

18.2.2.2.4 Mixed Hypoxia/Hypercarbia

Any disruption to airflow, parenchymal lung disease, or significant V/Q mismatch has the potential to lead to both hypoxia and hypercarbia. Marked hypercarbia itself can lead to hypoxia, as shown by the alveolar gas equation (Fig. 18.1). Ultimately, invasive ventilation is a mechanism to improve both ventilation and oxygenation in patients with derangements of gas exchange, regardless of the underlying cause. Inspiratory pressure, rate, and tidal volume are manipulated as the primary determinants of ventilation; while end-expiratory pressure, fraction of inspired oxygen, and inspiratory time primarily control oxygenation. Careful titration of these parameters is necessary to balance gas exchange and the underlying disease process while attempting to minimize ventilator-induced lung injury and the potential for hemodynamic compromise.

$$P_{A\text{O}_2} = F\text{I}\text{O}_2(P_{\text{ATM}} - P_{\text{H}_2\text{O}}) - \frac{P_{\text{a}}\text{CO}_2(1 - F\text{I}\text{O}_2(1 - RQ))}{RQ}$$

Fig. 18.1 The alveolar gas equation. $P_{A\text{O}_2}$ is alveolar partial pressure of oxygen, P_{ATM} is atmospheric pressure, $P_{\text{H}_2\text{O}}$ is the saturated vapor pressure of water, and RQ is respiratory quotient

18.2.2.3 Respiratory Muscle Insufficiency

Respiratory muscle insufficiency is the final common pathway necessitating invasive ventilation in a number of clinical conditions (Mehta 2006). The underlying weakness associated with these conditions and loss of airway reflexes frequently leads to a need for invasive ventilation. Regardless of whether the cause of respiratory failure is neuropathic or myopathic in origin, there are no significant differences in the resulting pathophysiologic state.

There are a number of congenital and inherited conditions that lead to weakness and place patients at significant risk for respiratory insufficiency and subsequently respiratory failure. Duchenne muscular dystrophy (DMD) is a condition affecting approximately 25/100,000 boys that is a representative example of a disease associated with progressive neuromuscular weakness and respiratory insufficiency (Kravitz 2009). Similarly, spinal muscular atrophy (SMA), affecting approximately 1 in 10,000 live births, is associated with progressive weakness and respiratory insufficiency (Mehta 2006). Children with conditions of this nature have impaired cough and secretion clearance secondary to underlying weakness, which creates significant lung volume loss and atelectasis. Progression of disease ultimately leads to the need for invasive ventilation, which may be implemented in this context secondary to either gradual progression or an acute respiratory insult.

Noninvasive ventilation is the preferred management of respiratory muscle insufficiency for most inherited diseases (Dohna-Schwake et al. 2008; Radunovic et al. 2009; Calderini et al. 2010), as the majority of these patients (1) require low levels of support, (2) often initially require support only during sleep, and (3) have a nonreversible process (Benditt 2009). For the patients who will either not tolerate noninvasive ventilation or will need increasing levels of support, most will progress to tracheostomy and home ventilation.

Acquired neuromuscular diseases can similarly lead to progressive respiratory failure secondary to weakness, but these illnesses most

Table 18.5 Neuromuscular causes of respiratory failure

Duchenne muscular dystrophy (DMD)
Becker muscular dystrophy
Spinal muscular atrophy (SMA)
Guillain-Barré syndrome (GBS)
Myasthenia gravis (MG)
Pompe's disease (glycogen storage disease II)
Clostridium botulinum infection
Corynebacterium diphtheriae infection
Tick paralysis
Periodic paralysis
Organophosphate poisoning
Muscle deconditioning due to chronic illness

often present acutely with rapid progression. Guillain-Barré syndrome presents as a progressive ascending paralysis and is the most common cause of acute respiratory failure secondary to neuromuscular disease in children (Mehta 2006). Myasthenia gravis may be acquired or congenital and similarly presents with weakness and respiratory failure. In addition, there are numerous other infectious, toxic, and metabolic conditions that affect the neuromuscular system that may lead to acute respiratory failure (Table 18.5). These acquired causes of respiratory muscle insufficiency are often temporary or reversible and may respond well to short-term invasive mechanical ventilation. These patients can usually be maintained on minimal support, and attention should be paid to avoiding ventilator-induced lung injury from overdistension due to large tidal volumes and/or high airway pressures.

18.2.2.4 Reduction of Mechanical load

18.2.2.4.1 Shock States

During times of critical illness, it may be necessary to minimize a patient's work of breathing to maximize oxygen delivery to vital organs. At baseline, less than 5 % of the body's oxygen consumption is required for breathing; however, in states of critical illness, this value can increase to 25–50 % (Lister and Current Concepts in Pediatric Critical Care 1992; Pinsky 2005). In cases of severe shock, where oxygen consumption exceeds oxygen delivery, the removal of this major source of oxygen consumption is often

necessary to maintain a safe tissue oxygen balance. The American College of Critical Care Medicine highlights this issue in their 2007 Pediatric Septic Shock Guidelines, recommending consideration of mechanical ventilation early in the course of shock (Brierley et al. 2009). Early intubation should allow providers to reach oxygen delivery goals associated with improved mortality in septic shock (Hazinski et al. 2002; Rivers et al. 2001).

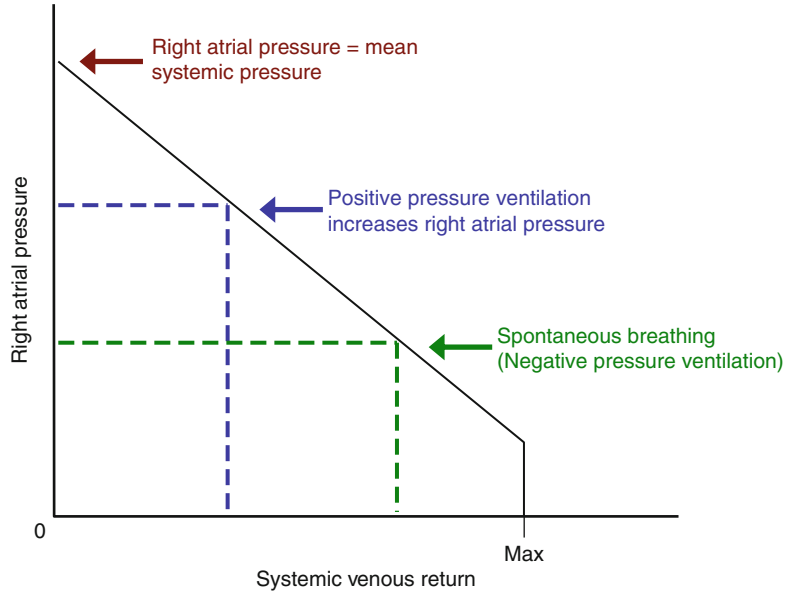
Pediatric patients with respiratory failure often are otherwise healthy, allowing them to maintain a natural airway and adequate gas exchange in a prolonged state of compensated shock. Unfortunately, some of these patients may experience a sudden respiratory decompensation after hours of relatively stable labored breathing. Providers must often rely on experience and clinical judgment, rather than laboratory data, to identify those patients who are in imminent respiratory collapse. For these patients, intervening in a controlled manner prior to cardiorespiratory collapse would be expected to provide superior outcomes (Topjian et al. 2008).

18.2.2.4.2 Cardiovascular Dysfunction

Another common indication for intubation and invasive mechanical ventilation is cardiovascular dysfunction, including cardiogenic shock. In the setting of impaired myocardial performance, invasive mechanical ventilation is often necessary to optimize gas exchange and decrease metabolic demands. Of importance, the initiation of positive pressure ventilation increases intrathoracic pressure (ITP), which can lead to dramatic alterations in cardiovascular performance due to changes in mechanical load on both the left and right ventricle (Pinsky and Summer 1983; Pinsky et al. 1983; Robotham et al. 1980).

Crucial differences exist in the impact of invasive mechanical ventilation on the right and left sides of the heart. The primary effect of increasing ITP on the right side of the heart is decreased preload to the right ventricle (RV). The increased intrathoracic pressures created by the initiation of positive pressure ventilation are transmitted to the right atrium, which impede venous return and decrease right ventricular (RV) preload (Fig. 18.2).

Fig. 18.2 Venous return versus intrathoracic pressure



This decrease in RV preload impairs RV performance by decreasing stroke volume and, thus, cardiac output (Robotham et al. 1980). There are potentially additional effects on intrinsic RV performance caused by increases in ITP, but in most physiologic circumstances, these are not clinically significant.

In addition to the effect on RV preload, the afterload on the RV must also be considered when invasive mechanical ventilation is initiated. Invasive ventilation has an important impact on pulmonary vascular resistance (PVR), which is the primary contributor to RV afterload. At low lung volumes, PVR is high due to the combination of autoregulatory hypoxic vasoconstriction and traction on the medium- and large-sized blood vessels supplying the lung. As lung volume increases toward functional residual capacity (FRC), PVR falls as these large- and medium-sized blood vessels expand and become less tortuous. Significantly above FRC, increases in lung volume lead to increases in PVR due to compression of the intra-alveolar capillaries by overexpanded alveoli (Fig. 18.3). Thus, as intrathoracic pressure and lung volume are manipulated, changes in PVR lead to variable effects on RV afterload and, subsequently, on RV output and global cardiac output.

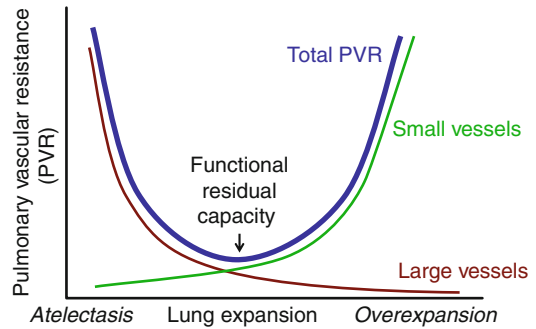


Fig. 18.3 Pulmonary vascular resistance versus lung volume

In addition to these RV effects, invasive ventilation impacts the left ventricle (LV) (Robotham et al. 1980). Increased ITP may lead to decreases in LV preload as in the RV, but the mechanisms of this change are less clear. By means of ventricular interdependence, RV stroke volume and direct LV compression likely contribute to decreased LV preload. In contrast, LV preload may be augmented in the setting of positive pressure ventilation via the “thoracic pump” mechanism. As intrathoracic pressure increases, the pressure in the pulmonary vasculature further exceeds left atrial pressure, creating a pressure gradient that augments left-sided preload and cardiac output (Pinsky and Summer 1983; Pinsky et al. 1983). It

must be stressed that this phenomena is clinically significant only at tidal volumes significantly higher than those currently used (i.e., >12 ml/kg).

LV afterload may be decreased by the initiation of positive pressure ventilation with its associated increase in ITP through a number of complex mechanisms. Due to the intricate interaction between myocardial wall tension and aortic autoregulation, increases in intrathoracic pressure decrease left ventricular afterload and augment cardiac output. This beneficial impact on the mechanical load of the left side of the heart is often an important consideration in the decision to initiate invasive ventilation in the setting of impaired myocardial performance (e.g., cardiomyopathy and myocarditis) and should also be considered when deciding on the timing of extubation in such a patient.

18.2.3 Assessment of the Need for Mechanical Ventilation

A meticulous physical examination and overall clinical assessment is the first step in establishing the need for intubation and invasive mechanical ventilation. Respiratory insufficiency may stem from neurologic, cardiac, neuromuscular, and/or respiratory dysfunction; each of these systems must be assessed to determine an individual patient's overall status and potential need for airway intervention and invasive ventilation. No single test is definitive in identifying a child who is in respiratory failure. The discretion of the bedside clinician is paramount in evaluating all available data in the context of an individual patient's clinical status. For example, common practice would dictate that a patient with a GCS of 7 be intubated; however, this may not apply to a developmentally delayed or a postictal patient. Similarly, a blood gas $p\text{CO}_2$ of 71 torr may have different implications for a child with status asthmaticus than for a teenager with end-stage cystic fibrosis.

Visual inspection of a child provides a wealth of clinical data: respiratory rate, work of breathing, level of anxiety, mental status, and inspiratory to expiratory ratio. In young children, it is often helpful to first monitor work of breathing

“from the doorway” as approaching the child will often provoke anxiety that may falsely worsen labored breathing. Increased respiratory effort may be manifested by tachypnea, increased use of accessory muscles, and increased inspiratory or expiratory force. These findings may also be associated with evidence of diminished respiratory effectiveness as demonstrated by decreased breath sounds on pulmonary examination. Careful auscultation may also provide clues to the underlying pathophysiology.

Adequate airway assessment is paramount, beginning with an appraisal of airway patency, followed by an assessment of the factors that may contribute to difficulty with endotracheal tube placement, including an underlying diagnosis known to be associated with airway difficulties (Table 18.1), history of difficult airway management, limitation of neck extension, limited mouth opening, short thyromental distance, and midface hypoplasia (Santillanes and Gausche-Hill 2008). Even though the incidence of failed airway management in children is rare, this evaluation can be quickly completed and allows for preparation and mobilization of additional resources which may be necessary to manage the difficult airway. Appropriate assessment and planning may help to avoid an airway disaster.

Following airway assessment, an evaluation of the adequacy of respiratory reflexes, drive, effort, and capacity is critical. Neurologic dysfunction or injury may lead to inadequate airway reflexes, placing the patient at risk for aspiration and progression of respiratory insufficiency if invasive ventilation is not initiated. All of this clinical information should be carefully considered and followed over time given the often rapid progression among children from respiratory distress to respiratory failure.

Circulatory and cardiovascular assessment is an additional important element of the determination of the need for invasive ventilation. Tachycardia is common in the setting of respiratory distress and impending respiratory failure. Additionally, hypoxia leads to inadequate oxygen delivery and metabolic acidosis, which can have negative impacts on cardiac performance and overall organ and tissue perfusion. Initiation

of mechanical ventilation can substantially decrease metabolic demands and improve the balance between oxygen supply and consumption. However, cardiopulmonary interactions created by the implementation of positive pressure ventilation should be carefully considered in patients with developing hemodynamic instability as discussed earlier in this chapter.

In addition to physical examination, the chest radiograph (CXR) is an important adjunctive examination in assessing the need for mechanical ventilation. The CXR is rarely solely diagnostic but may provide insight into both the severity and underlying etiology for respiratory distress/failure. Assessing serial CXRs may assist in guiding therapeutic interventions and mechanical ventilatory strategies. Assessment of the CXR should involve a systematic approach that evaluates all aspects of the radiograph to prevent omission of identifying abnormalities. It is also important to note that CXR findings usually lag behind clinical findings to some degree, limiting their usefulness in some circumstances. Overall, the CXR should be taken in the context of the global clinical situation. In certain cases, further imaging, such as chest ultrasound or computed tomography (CT) scan may be necessary to confirm a diagnosis.

Bedside monitoring of adequate oxygenation is usually accomplished using standard pulse oximetry; however, in cases of suspected carbon monoxide poisoning or methemoglobinemia, a blood gas analysis with co-oximetry will be required to accurately measure oxygen saturation as the presence of carboxyhemoglobin or methemoglobin interferes with the wavelength analysis of a standard pulse oximeter.

Arterial blood gas sampling provides information regarding adequacy of gas exchange, acid-base status, and acuity of disease onset, all of which are important data points that may also be followed over time. Other methods of blood gas sampling (e.g., capillary or venous) may provide an estimate of acid-base status but should be used with caution when assessing effectiveness of oxygenation. Markers of global stability such as serum lactate, electrolytes, and blood cell counts

may also provide clinicians a sense of the patient's overall status and may help direct the timing of interventions.

The need for invasive mechanical ventilation may depend more on a patient's illness trajectory than clinical status at any one moment in time. A patient who has resolving altered mental status may avoid an unnecessary intubation; while intervening early for a child whose condition is deteriorating may prevent cardiorespiratory instability and collapse. Finally, for terminal illnesses, it is appropriate to consider not initiating invasive mechanical ventilation if it is highly unlikely that the child will be able to be weaned from the ventilator and the parent(s)/guardian(s) request limitations of life support. It is often beneficial to begin this discussion with the family and, if developmentally appropriate, the child, before an emergent need for mechanical ventilation arises.

Artificial ventilation is not curative; it is a supportive measure, giving the patient time to recover from a pulmonary and/or systemic insult. Due to risks of clinical instability during the intubation procedure, airway trauma, ventilator-induced lung injury, and ventilator-associated pneumonia, clinicians must consider available alternatives to invasive mechanical ventilation. For example, quickly reversible diseases, such as opioid overdose, may require temporary bag-mask ventilation while an antidote is administered.

There are also many circumstances in which invasive mechanical ventilation may be avoided by the utilization of noninvasive ventilation (NIV). Even in the setting of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), patients can be effectively and successfully treated with NIV (Calderini et al. 2010; Flori et al. 2005). However, the use of NIV in pediatrics can be complicated by difficulties with both the patient interface and patient cooperation, thus, potentially necessitating invasive ventilatory support. Also, once it is clear that a patient will need invasive ventilation, efforts should be focused on placement of an advanced airway in the safest manner possible – specifically, noninvasive ventilation should not be used to prolong

unavoidable intubation (Nava and Hill 2009; Yanez et al. 2008).

The decision to initiate mechanical ventilation involves a number of important considerations. Multiple organ systems should be included in the pre-ventilation assessment of the patient, and initiation of therapy for the underlying etiology for respiratory distress should also be quickly implemented. As the decision is made to initiate ventilation, the complex interactions created by positive pressure ventilation must be anticipated. The choices of ventilatory modes and initial settings are detailed in a separate chapter in this textbook.

18.2.4 Cautions and Contraindications to Invasive Mechanical Ventilation

Short of brain death, there are no absolute contraindications to invasive mechanical ventilation in children. Relative contraindications center on the use of invasive ventilation in patients when invasive ventilation may worsen a patient's clinical status or prolong death in the setting of a terminal illness. Alternative methods of ventilating patients (i.e., noninvasive ventilation) are being employed at an increasing rate in the pediatric critical care setting.

Cystic fibrosis, severe bronchospasm, and status asthmaticus (as discussed earlier in this chapter) are situations in which dynamic hyperinflation and air trapping may be significantly exacerbated by the initiation of positive pressure ventilation. In these circumstances, it is often difficult or impossible to invasively ventilate the patient as effectively as when they are breathing spontaneously, even in the setting of impending respiratory failure. In addition, invasive ventilation in this context can create significant hemodynamic compromise and may precipitate cardiopulmonary collapse and possibly arrest due to inadequate systemic venous return and, subsequently, depressed cardiac output. However, even in these settings, invasive ventilation may represent the best opportunity

for survival and should be implemented as clinically indicated based on the risk/benefit assessment of the medical care team.

Another circumstance in which caution should be undertaken when initiating invasive ventilation is in the setting of severe shock. Intubation is clearly indicated in this circumstance to decrease metabolic demands and improve the balance between oxygen delivery and consumption, but the initiation of positive pressure ventilation in this setting can have profound negative impacts on a patient's hemodynamic status. Augmentation of intravascular volume status (i.e., preload) is of importance in this setting to prevent cardiovascular collapse following intubation. Similarly, patients who have undergone palliative surgery for congenital heart disease resulting in passive pulmonary blood flow (e.g., patients who are status post Glenn or Fontan operations) are also at risk for hemodynamic deterioration in the setting of positive pressure ventilation due to diminished pulmonary blood flow and cardiac output as intrathoracic pressure is increased.

In the case of a terminal or nonreversible condition, the medical team, along with the family and, if appropriate, the patient, must decide if invasive mechanical ventilation is in the best interest of the patient. Invasive mechanical ventilation should not be used to prolong the dying process but may be appropriate if requested by the patient's parent(s)/guardian(s), especially if it allows optimization of comfort, either for removing air hunger or enhancing pain control.

While many critically ill pediatric patients develop a need for invasive mechanical ventilation, securing the airway and initiating ventilation should be accomplished as safely as possible. Placement of advanced airways may be difficult in pediatric patients, with potentially disastrous results if the patient's airway cannot be appropriately maintained and/or if positive pressure ventilation has negative effects on cardiac or respiratory physiology. For these reasons, we recommend that whenever possible, initiation of invasive mechanical ventilation of a pediatric patient be performed with the support of medical

care providers with experience in both pediatric airways and ventilation of infants/children.

18.2.5 Short- and Long-Term Outcomes

Fortunately, pediatric patients admitted to intensive care units have a very low mortality, typically less than 5 % at baseline (Odetola et al. 2008). However, due to their intrinsically smaller airways, infants and children are more likely to suffer complications and morbidities related to the endotracheal tube and invasive ventilation. The incidence of subglottic stenosis in children following intubation is reported to be 1–10 %, but with recent advances in technology, it is likely closer to 2 % (Mossad and Youssef 2009; Walner et al. 2001). Children less than 1 year of age and those with prolonged courses of mechanical ventilation are at an increased risk for subglottic stenosis. Recent data show that the presence of a tracheal cuff is likely not a risk factor for subglottic stenosis (Mossad and Youssef 2009). Other complications of endotracheal intubation in children include paralyzed vocal cord or direct vocal cord trauma, tracheal tears, and subglottic or glottic cysts or polyps (Miller et al. 2009). Malpositioning of the endotracheal tube may lead to pneumothorax, single lung collapse and worsened gas exchange, or damage to the bronchus.

Outside of premature infants, who may still face significant chronic lung disease and bronchopulmonary dysplasia, long-term morbidity is low among mechanically ventilated pediatric patients; however, a paucity of data exist examining long-term pulmonary, neurologic, and quality of life outcomes in ventilated children. Collecting these data is problematic because of the largely heterogeneous population among all ventilated infants and children.

Among children who are mechanically ventilated for all causes, approximately 9 % develop acute lung injury (ALI) (Dahlem et al. 2007). For the majority of children with ALI who did not progress to ARDS, mortality is low at 3–11 % (Dahlem et al. 2007). However, mortality is

significantly higher for children with ARDS at 10–30 % (Randolph 2009; Prodhan and Noviski 2004), but this is significantly better than for adults with ARDS, whose mortality is estimated between 30 and 50 % (The Acute Respiratory Distress Syndrome Network 2000; Brower et al. 2001).

Unlike adults, the degree of hypoxia has been demonstrated as a potential predictor of mortality in the pediatric population. Worse initial P_aO_2/FiO_2 (P/F) ratio and presence of multiorgan failure are each independent predictors of mortality across multiple studies. Mortality was also demonstrated in one study to increase from 20 to 36 % for patients with an Oxygenation Index (OI; calculated as $P_{AW} \times FiO_2/P_aO_2$) greater than or equal to 13 when compared to those with an OI of 12 or less (Willson et al. 2005). Higher pediatric risk of mortality (PRISM) scores and initial oxygenation indices have also been shown to predict mortality (Randolph 2009). Continued assessment of markers such as this is an important aspect of the management of pediatric respiratory failure as practitioners attempt to guide clinical practice.

Certain populations are at markedly increased risk for mortality, none more so than children after hematopoietic stem cell transplantation, whose mortality with ALI is generally greater than 75 % and approaches 100 % with prolonged ventilation and multiorgan involvement (Randolph 2009; Martin 2006). Other children with immune deficiencies and comorbid medical conditions are also at higher risk; however, reported mortality rates vary greatly due to small numbers of patients studied and widely varying clinical practice.

Historically, pediatric ARDS patients requiring ECMO have also had better survival rates than adults. Early Extracorporeal Life Support Organization (ELSO) data on 1,000 patients on ECMO for respiratory failure at the University of Michigan showed 88 % survival to hospital discharge for neonates, compared to 70 % survival for pediatric patients, and 56 % survival for adults (Bartlett 1997; Marasco et al. 2008). However, recent ELSO data indicate survival to discharge of 75, 56, and 52 %

Essentials to Remember

- Airway management is a critical element of caring for critical illness, and a global assessment involving all organ systems is crucial in the assessment of a patient's airway status.
- Initiation of ventilation in pediatrics represents a balance between the underlying disease and the state of physiologic development.
- Inadequate gas exchange is the most common indication for mechanical ventilation.
- Neurologic dysfunction frequently necessitates invasive ventilation.
- Mechanical ventilation creates significant cardiopulmonary interactions which principally include decreased right ventricular preload and decreased left ventricular afterload.
- Special consideration of risks and potential complications of mechanical ventilation should be made in the setting of asthma, severe bronchospasm, passive pulmonary blood flow, and severe shock.
- Outcomes for infants and children requiring mechanical ventilation are generally favorable, usually matching or exceeding outcomes of adult counterparts.

for neonates, pediatrics, and adults, respectively, showing similar survival rates for all patients outside of the neonatal period (Extracorporeal Life Support Organization 2010). Decreased survival rates in the more recent data may correlate with a trend of using ECMO for an increasingly sicker patient population. Patients on ECMO for primary cardiac diagnoses consistently have a 10–40 % higher mortality than noncardiac ECMO patients (Bartlett 1997; Extracorporeal Life Support Organization 2010; Cook 2004).

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19.1 High-Frequency Ventilation

19.1.1 High-Frequency Oscillatory Ventilation (HFOV)

Casper Bollen and Peter C. Rimensberger

Educational Aims

- Understand essential mechanics of HFOV.
- Understand causes of ventilator-induced lung injury.
- Be able to translate this knowledge into ventilation strategies that aim to minimize deleterious effects of mechanical ventilation.
- Know the characteristics of HFOV that help to prevent ventilator-induced lung injury.
- Know the evidence for choosing HFOV as an elective therapy.
- Know the evidence for choosing HFOV as a rescue therapy.
- Be able to assess which patients will benefit from HFOV based on theory and evidence.
- Know which patients are eligible for HFOV in the neonatal intensive care unit.
- Know which patients are eligible for HFOV in the pediatric intensive care unit.

19.1.1.1 Introduction

Critical care physicians facing patients that require invasive mechanical ventilation are confronted with the questions what type of ventilator and what ventilator strategy is most appropriate for this particular patient. Mechanical ventilation is initiated to bridge a gap to recovery or to supply chronic support. Failure of mechanical ventilation can arise through inability to deliver adequate gas exchange or through resulting complications, like pneumothorax. Although mechanical ventilation is meant to support respiratory function, mechanical ventilation can also result in pulmonary damage and contribute to increased risk of mortality. Therefore, the selection of the ventilator type and strategy should be guided by the capacity to achieve adequate gas exchange and, in the meanwhile, to prevent lung injury.

The two basic types of ventilators that can be considered to achieve these goals are the conventional mechanical ventilator or one of several types of high-frequency ventilators. In this section we will focus on high-frequency oscillatory ventilators (HFOV). Using conventional mechanical ventilation (CMV), tidal volumes at more or less physiological breathing rates are delivered, while with high-frequency oscillatory ventilation (HFOV), respiratory rates are employed far above the physiological range.

Up till now CMV is standard of care. The indications to use HFOV can be classified into two categories: (1) rescue indications, i.e., when CMV fails to sustain adequate gas exchange or leads to major complications, or

(2) elective indications, i.e., in which it is anticipated that use of HFOV improves overall prognosis compared to HFOV. Treatment failure of CMV can reveal itself by insufficient carbon dioxide elimination despite high tidal volumes or impaired oxygenation despite high fractional inspiratory oxygen and high mean airway pressure. Failure to support gas exchange can be addressed by providing additional measures like nitric oxide inhalation or prone positioning. Alternative therapies can be considered next, like HFOV or ultimately lung replacement therapies like extracorporeal membrane oxygenation. Ventilation-associated complications like air leak syndromes or cardiovascular compromise can also prompt for these alternative therapies.

To understand the rationale for choosing HFOV as an alternative therapy for HFOV, two important aspects of mechanical ventilation have to be recognized. First, over the past decades, it has become apparent that mechanical ventilation can have deleterious effects both locally, resulting in lung damage, and systematically, resulting in increased mortality. Secondly, the effects of mechanical ventilation are more importantly determined by ventilation strategy than by the type of ventilator that is used. Optimal ventilation strategy is determined by patient features and by disease characteristics. The type of ventilator can enable or constraint application of ventilation strategy.

19.1.1.2 Educational Aims

In this chapter, we will discuss indications for HFOV. Why and when should HFOV be considered and in which neonatal and pediatric patients? The answers to those questions are closely connected to theories and evidence concerning ventilator-induced lung injury and lung protective ventilation strategies to prevent lung injury. Therefore, it is important to understand the concepts of ventilator-induced lung injury and how this translates to lung protective ventilation strategies.

The rationale for choosing HFOV instead of CMV will focus on the differences between these two modes of ventilation that will facilitate use of a lung protective ventilation strategy.

19.1.1.3 Pathophysiological Rationale for Choosing HFOV

19.1.1.3.1 What Is HFOV?

19.1.1.3.1.1 HFOV Characteristics

HFOV can be described by the following characteristics: (1) ventilation at high respiratory rate, generally 3–25 Hz; (2) use of a continuous distending airway pressure; (3) superimposed ventilation with small tidal volumes, typically less than anatomical dead space; and (4), specifically for HFOV, an active expiration phase. In other types of high-frequency ventilation, the expiration phase is mainly passive.

HFOV employs a piston or diaphragm to oscillate a bias flow of gas (between 10 and 40 l, according to patient size and demands) to produce alternating positive- and negative-pressure swings. A continuous distending pressure is generated by a low-pass filter that acts as a resistor. HFOV is unique in its active expiration phase created by the backward movement of the diaphragm that generates a negative pressure.

19.1.1.3.1.2 HFOV Operation and Gas Exchange

Operator-selected parameters include adjustment of the following: mean airway pressure (continuous distending pressure), frequency, inspiratory time, pressure amplitude, bias flow, and oxygen concentration of inspired gas. Like in CMV, to improve oxygenation, mean airway pressure is increased. However, in HFOV, regulation of oxygenation is uncoupled from carbon dioxide elimination, i.e., adjustment of the mean airway pressure does not necessarily affect carbon dioxide elimination. Moreover, by decreasing frequency, unlike in CMV, carbon dioxide elimination is increased and vice versa. Inspiratory time can be adjusted to improve oxygenation but is typically set at 33 %. The amplitude can be adjusted upward and downward to

increase and decrease carbon dioxide elimination, respectively. Bias flow can be adjusted to maintain mean airway pressure and depends on patient size and demands.

During CMV, carbon dioxide removal is accomplished by bulk convection and is directly related to minute ventilation, the product of tidal volume and frequency. HFOV achieves gas transport with tidal volumes that are below anatomic dead space; therefore, carbon dioxide must be “washed out” by additional mechanisms. In HFOV, carbon dioxide elimination is directly related to ventilatory frequency and the square of delivered volume that is a function of amplitude. Because of the technical characteristics of the device, the delivered volume is inversely related to frequency. Frequency controls the time allowed for the piston to move, i.e., the lower the frequency, the greater the volume displacement and vice versa. It is recommended to set the amplitude at the highest possible pressure and adjust the frequency accordingly. This will result in the highest possible frequency as well, as frequency and pressure amplitude have an inverse effect on carbon dioxide elimination (Fessler et al. 2007; Froese 1997; Hager et al. 2007).

19.1.1.3.1.3 Other Types of High-Frequency Ventilation

There are four major types of high-frequency ventilation: (1) high-frequency positive-pressure ventilation (frequency 1–2.5 Hz), (2) high-frequency jet ventilation (frequency 1.7–10 Hz), (3) high-frequency flow interruption (6–15 Hz), and (4) high-frequency oscillatory ventilation (HFOV, frequency 3–15 Hz). High-frequency positive-pressure ventilation and high-frequency jet ventilation promote gas exchange in a more conventional way, i.e., tidal volumes approximate or exceed dead space volume, and expiration is passive. In contrast, in HFOV tidal volumes are generated that are less than dead space and expiration phase is active. It has been estimated that tidal volumes delivered during

HFOV are about 1–4 mL/kg, depending on frequency (Sedeek et al. 2003). HFOV is now the most commonly used method of high-frequency ventilation with a good and long-standing experience in neonatal and pediatric intensive care (Rimensberger 2003).

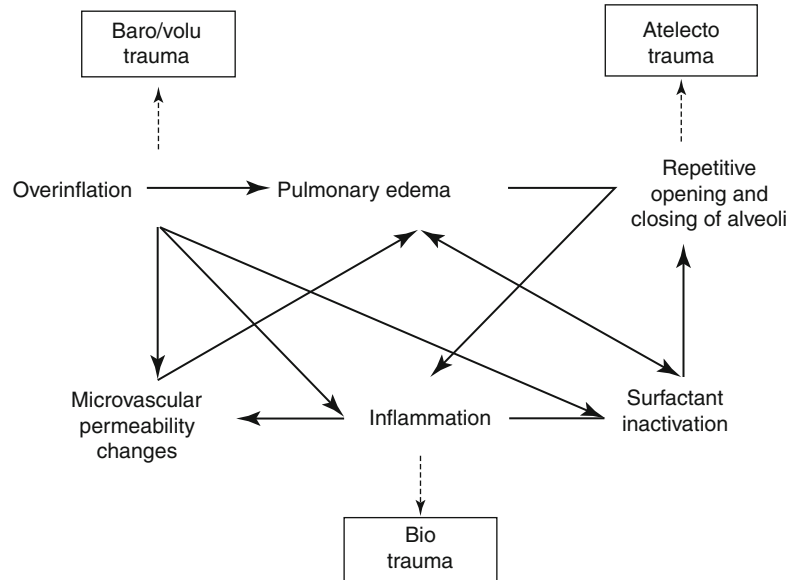
19.1.1.3.2 What Factors Cause Ventilator-Induced Lung Injury?

The injurious effects of mechanical ventilation on lung tissue have been designated as ventilator-induced lung injury (Dreyfuss and Saumon 1998; Pingleton 1988). Ventilator-induced lung injury is a concept that has been extensively investigated in animal experimental studies. It represents a complex disorder that is caused by a number of ventilator-related factors. These main explanatory mechanisms have been called barotrauma, volutrauma, atelectotrauma, and bio-trauma (Fig. 19.1) (Dreyfuss and Saumon 1992, 1998; Parker et al. 1993).

19.1.1.3.2.1 Barotrauma and Volutrauma

Historically, attention was focused on clinically apparent barotrauma, represented by air leak syndromes. Webb et al. were the first to demonstrate experimental evidence that high airway pressures could lead to increased capillary permeability, non-hydrostatic pulmonary edema, and tissue damage (Webb and Tierney 1974). Subsequent studies showed that ventilation with large tidal volumes had more impact on the occurrence of ventilator-induced lung injury than high airway pressures on itself (Carlton et al. 1990; Dreyfuss et al. 1992; Hernandez et al. 1989). Therefore, it has been advocated to replace the term “barotrauma” by “volutrauma” (Dreyfuss and Saumon 1992). The basic premise is that high tidal volumes (volutrauma) cause overdistension of alveoli, which is associated with increased capillary permeability, pulmonary edema, and histological damage (Carlton et al. 1990; Dreyfuss et al. 1985; Kim and Crandall 1982; Parker et al. 1984, 1990).

Fig. 19.1 Pathophysiological mechanisms of ventilator-induced lung injury. Three major mechanisms lead to ventilator-induced lung injury: (1) barotrauma/volutrauma, (2) atelectotrauma, and (3) biotrauma. There is a reinforcing interaction between the different mechanisms leading to a number of vicious circles. See text for further explanation



19.1.1.3.2.2 Atelectotrauma

Another putative mechanism causing ventilator-induced lung injury is the concept of “atelectotrauma.” Atelectotrauma is thought to be caused by repetitive opening and closing of alveoli resulting in shear stress and mechanical damage, especially in already diseased parts of the lung (Muscedere et al. 1994; Sohma et al. 1992; Taskar et al. 1997). In the previously mentioned study by Webb et al., it was already demonstrated that positive end-expiratory pressure as opposed to zero end-expiratory pressure had a protective effect (Webb and Tierney 1974).

19.1.1.3.2.3 Biotrauma

Finally, prolonged injurious ventilation results in microscopic abnormalities with inflammatory infiltrates that are indistinguishable from acute respiratory distress syndrome in humans (Kawano et al. 1987; Tsuno et al. 1991). Experimental studies showed a distinctive effect of ventilation strategy on cytokine concentrations in lung lavage (Tremblay et al. 1997). Harmful ventilation strategies were associated with major increases in cytokine concentrations. The term “biotrauma” has been coined to describe poten-

tially injurious local and systematic inflammatory response to physiological stress.

Putting it all together, the sequence of events resulting in ventilator-induced lung injury can be described as depicted in Fig. 19.1.

19.1.1.3.3 Ventilation Strategies That Prevent Ventilator-Induced Lung Injury

Lung protective ventilation strategies specifically aim to prevent ventilator-induced lung injury. In both HFOV and CMV, these strategies rely on the same principles: recruitment and prevention of subsequent de-recruitment of alveoli while at the same time avoidance of overdistension. The concept of a lung protective ventilation strategy can be visualized by the pressure-volume curve. In this curve, a “safe window” seems to exist (see Fig. 13.1) (Froese 1997). This means that level of positive end-expiratory pressure must be sufficiently high to prevent de-recruitment and atelectasis on the one end and on the other end the peak inspiratory pressure superimposed on the positive end-expiratory pressure should not result in overdistension. The price of limiting tidal volumes to achieve this goal may be hypercapnia.

19.1.1.3.3.1 Prevention of Atelectasis

Prevention of atelectasis has been expressed as “open up the lung and keep the lung open” (Lachmann 1992). This implies that a sufficient amount of airway pressure is needed to maintain patency of the airways and alveoli. Positive end-expiratory pressure is pivotal in this concept and defines the lower limit of the pressure swings that can be applied in a lung protective ventilation strategy.

19.1.1.3.3.2 Prevention of Overdistension

Overdistension of alveoli has received attention first by limiting inspiratory pressures. More recently, emphasis has been put on limiting tidal volumes. Still, inspiratory pressures remain important proxies to estimate the level of overdistension. High positive pressure combined with limitation of inspiratory pressure results in even smaller tidal volumes to meet the demands of lung protective ventilation. In CMV, hypercapnia and respiratory acidosis will limit the feasibility to achieve the objectives of lung protective ventilation strategies.

19.1.1.3.3.3 Resulting Hypercapnia

The resulting hypercapnia, however, has been proposed to have an independent lung protective effect. It is unknown if hypercapnia can be considered as an acceptable side effect of a lung protective ventilation strategy or if it should be implemented in a lung protective ventilation strategy to strive for as an independent goal (Feihl and Perret 1994).

19.1.1.3.4 How Does HFOV Prevent Ventilation-Induced Lung Injury?

The lung protective ventilation strategy used in HFOV has been qualified as “high lung volume strategy.” A high lung volume strategy consists of the following approaches: (1) use of a higher mean airway pressure than on CMV, (2) initial weaning of fractional inspired oxygen before decreasing mean airway pressure, and (3) use of alveolar recruitment maneuvers. Fractional inspired oxygen is considered to be a useful clinical

parameter to assess lung volume recruitment. Optimal recruitment is reflected by a fractional inspired oxygen which can be weaned below 0.30 or even 0.25.

19.1.1.3.4.1 Recruitment “Open Up the Lungs”

Recruitment of non-aerated lung tissue has become one of the three cornerstones of lung protective ventilation (Clark et al. 2000; Gattinoni et al. 2003). In applying an open-lung strategy, mean airway pressure is gradually increased by steps of 1–2 cm H₂O, with the goal of reducing fractional inspired oxygen to less than 0.60–0.40. Oxygen saturation should remain above 90 % (or equal to 85 % in the premature infant). During this phase hemodynamics should be carefully monitored. Central venous pressure in pediatric patients should be maintained at a level sufficient to overcome mean airway pressure, typically around 10–15 mmHg (Arnold et al. 1994). In pediatric patients, additional inotropic support should be considered as well. In premature infants, at the occurrence of a minimal decrease of blood pressure (i.e., more than 2 mmHg), airway pressures should be reduced and the oxygen response conserved before eventually further increasing airway pressures again.

19.1.1.3.4.2 Optimizing Mean Airway Pressure “Keep the Lungs Open”

After recruitment, once appropriate saturation is achieved and fractional inspired oxygen can be lowered to less than or equal to 0.6, airway pressure should be reduced stepwise in decrements of 1–2 cm H₂O (moving downward on the deflation limb of the pressure-volume curve that exhibits hysteresis) (Mehta et al. 2001; Rimensberger et al. 1999). As long as oxygen saturation can be maintained, airway pressure can be further decreased, until the lowest pressure is reached that ensures adequate saturation. Chest radiography is recommended after finding the optimal mean airway pressure to assess adequacy of lung recruitment and to exclude signs of overinflation. If signs of overinflation are present, airway pressures should be reduced even further.

19.1.1.3.4.3 Limiting Tidal Volumes “Prevent Overdistension”

In CMV, small tidal volume ventilation may cause complications resulting from the effects of acute respiratory acidosis on hemodynamics, gas exchange, and oxygen transport or consumption (Crotti et al. 2001) that require an increased use of sedatives and often muscle relaxants, and may lead to alveolar instability and lung collapse (Carvalho et al. 1997). Within the context of ventilator-induced lung injury and lung protective strategies, HFOV could be considered to be the most optimal protective ventilator mode, providing by design small tidal volume ventilation and facilitating lung recruitment and maintenance of optimal lung volume without concomitant lung overdistension (Ferguson and Slutsky 2008). However, there is ongoing debate whether this translates to better clinical outcome.

19.1.1.4 Elective vs. Rescue HFOV

Indications for HFOV can be divided in:

1. Rescue indications: in which CMV is unable to maintain adequate gas exchange or has resulted in major complications
2. Elective indications: in which HFOV is selected as the initial choice of treatment based on the expected improvement in clinical outcome as compared to CMV as an initial treatment choice

There is a tension between selecting HFOV as a rescue treatment and HFOV as a first-choice treatment. It has been argued that delayed use of HFOV in very low-birth-weight infants precluded the beneficial effects, as lung injury already might have occurred on CMV (Rimensberger et al. 2000). This has not been confirmed in meta-analysis of trials comparing HFOV with CMV in premature neonates (Bollen et al. 2007). In a meta-analysis of trials in adult patients with acute respiratory distress syndrome, duration on CMV prior to HFOV was not associated with outcome either (Bollen et al. 2006). However, in an individual patient data meta-analysis, the timing of

initiation of HFOV has been suggested as a modifying factor of the relative treatment effect in a selected patient group of premature infants.

The ideal timing of HFOV, to make a difference with CMV, will be determined by the risk of ventilator-induced lung injury at a time lung injury has not occurred yet. At the extremes there are patients that are not at risk of ventilator-induced lung injury, and there are patients in whom poor pulmonary outcome cannot be avoided. HFOV will not exhibit any advantageous effects over CMV in these patients. Therefore, prognostic factors of ventilator-induced lung injury could serve as important indicators to initiate HFOV. It has been suggested that these markers relate to the inability of CMV to maintain tidal volumes within the safe window of the pressure-volume curve while preserving adequate gas exchange (Bollen et al. 2008).

19.1.1.5 Choosing the Right Patient for HFOV

19.1.1.5.1 Is Recruitment Possible?

Adult and newborn animal studies have shown that the full potential of attenuating ventilator-induced lung injury will only be reached if HFOV is combined with optimal recruitment and stabilization of previously atelectatic lung units (Kolton et al. 1982; McCulloch et al. 1988; Meredith et al. 1989). One of the major “handicaps” in optimizing recruitment or lung volume during HFOV in clinical practice is the inability to accurately measure direct changes in lung volume at the bedside (Hulskamp et al. 2006). Animal studies suggested that oxygenation can be used as an indirect measure of change in lung volume (Suzuki et al. 1992; van Genderingen et al. 2004). The relative benefit of HFOV over CMV could be determined by the extent to which optimization of recruitment and change of lung volume, i.e., oxygenation, is feasible in the individual patient. In patients with lungs that cannot be recruited, so-called baby lungs (Gattinoni et al. 2004), HFOV could prevent overdistension while providing adequate ventilation as compared to CMV.

19.1.1.5.2 The Importance of Ventilation Strategies

Specific lung protective ventilation strategies utilized in CMV can reduce chronic lung disease. Treatment strategies and their effects on lung injury are based on pathophysiological studies in animal models, showing increased cytokine release with higher tidal volumes and reduced positive end-expiratory pressure (Meredith et al. 1989), or trials in adults with respiratory distress syndrome (Petrucci and Iacovelli 2007). Allowing carbon dioxide to rise, permissive hypercapnia, rather than increasing ventilation reduces lung injury in preterm infants (Woodgate and Davies 2001). Strategies to synchronize ventilation using higher respiratory rates and patient-triggered ventilation also reduce the rate of pneumothorax and the duration of ventilation (Greenough et al. 2008).

Clark et al. pointed out the importance of ventilation strategies employed in HFOV and CMV to compare the relative treatment effect of reducing lung injury (Clark et al. 2000). The importance of ventilation strategies, as such, compared to the type of ventilator that delivers these strategies has been demonstrated in a cumulative meta-analysis of trials in premature infants (Bollen et al. 2003). In this study, the modifying effects on the relative treatment benefit of HFOV over CMV of ventilation strategies and concomitant treatment were shown. Enhancements of CMV over the years have diminished the relative treatment benefits of HFOV.

19.1.1.5.3 Classical Indications for HFOV in Neonatal and Pediatric Patients

Classical indications for HFOV in the neonatal population are as follows: respiratory distress syndrome, congenital diaphragmatic hernia, air leak syndrome, and persistent pulmonary hypertension of the newborn (Bryan and Cox 1999; Nobuhara and Wilson 1996). Classical indications for HFOV in the pediatric population include diffuse alveolar disease (e.g., primary or secondary acute respiratory distress syndrome) (Arnold et al. 1994), with growing experiences of lower airway disease, at

least when conventional ventilation fails (bronchiolitis, status asthmaticus, and acute chest syndrome) (Berner et al. 2008; Wratney et al. 2004; Duval and van Vught 2000; Duval et al. 2000).

19.1.1.5.4 Indications in Adult Patients

Evidence obtained in adult patients can be of considerable relevance to larger pediatric patients. HFOV has been used in adults for a variety of indications. The most important indication for HFOV is acute respiratory distress syndrome as in pediatric patients (Mehta et al. 2001; Derdak et al. 2002; Fort et al. 1997). Chan et al. summarized the evidence of use of HFOV in adult patients with acute respiratory distress syndrome (Chan et al. 2007). They concluded that many questions remained unanswered and, given the substantial mortality reductions with current CMV based lung protective strategies, HFOV should be compared to CMV in a large randomized trial with mortality as the primary outcome measure.

Table 19.1 summarized the different indications for HFOV in specific patient groups along with the levels of evidence that support these indications.

19.1.1.6 HFOV in the Neonatal Intensive Care Unit

19.1.1.6.1 Elective HFOV in Respiratory Distress Syndrome

19.1.1.6.1.1 Short-Term Outcome

Pulmonary disease continues to be a major cause of morbidity and mortality in very preterm infants. Although CMV has decreased mortality, morbidity from lung injury remains high. Acute injury such as pulmonary air leak was common prior to the availability of surfactant. However, chronic lung disease still develops in up to one third of preterm infants with respiratory distress syndrome who require mechanical ventilation (Lemons et al. 2001; Northway 1992). In addition to immaturity, overdistension of the lung and oxygen toxicity are considered to be important causal factors in the pathogenesis of chronic lung disease (Jobe and Ikegami 2000).

Table 19.1 Levels of evidence to use HFOV instead of CMV

Indication	Patients	Type of use	Clinical effect	Level of evidence	References
Respiratory distress syndrome	Preterm neonates	Elective	Reduction of chronic lung disease, estimated number to treat = 25	I-A	Courtney et al. (2002), Johnson et al. (2002), Cools et al. (2009)
			Long-term outcome is similar with respect to pulmonary function and neurodevelopmental outcome	I-B	Truffert et al. (2007), Marlow et al. (2006), Gerstmann et al. (2001), Thomas et al. (2004)
		Rescue	There is insufficient evidence to estimate the clinical effect of rescue HFOV in preterm neonates	I-B	HiFO Study Group (1993), Bhuta and Henderson-Smart (2000)
Pulmonary dysfunction	Term or near-term neonates	Rescue	Successful weaning from mechanical ventilation with HFOV after failure of HFOV	III	Ben et al. (2006a)
			No clinical benefit with or differences in treatment failure between HFOV and CMV	I-A	Clark et al. (1994), Henderson-Smart et al. (2009), Rojas et al. (2005)
		Elective	Improvement of survival has been recorded in selected patients	III	Datin-Dorriere et al. (2008), Migliazza et al. (2007)
Severe pulmonary hypertension	Neonates	Rescue	HFOV combined with inhaled nitric oxide could prevent ECMO. However, benefit over CMV with inhaled nitric oxide has not been demonstrated	I-A	Kinsella et al. (1997a)
Acute respiratory distress syndrome	Pediatric patients	Rescue	Improvement in oxygenation and reduced need for oxygen at 30 days, but no reduction in mortality	I-B	Arnold et al. (1994)
		Rescue	No significant reduction in mortality. However, there is improvement in short-term oxygenation and there is a trend toward reduced mortality	I-A	Arnold et al. (1994), Derdak et al. (2002), Bollen et al. (2005), Wunsch and Mapstone (2004)
Small airway disease	Pediatric patients	Rescue	Achieving adequate gas exchange in selected patients when CMV fails	III	Berner et al. (2008), Duval and van Vught (2000), Kneyber et al. (2005), Thompson et al. (1995), Medbo et al. (1997), Duval et al. (1999), Seferian et al. (2006), Slec-Wijffels et al. (2005)

Asymmetric lung injury	Pediatric and adult patients	Rescue	HFOV is feasible in asymmetric lung injury. However, clinical benefit is unknown	III	Terragni et al. (2005), Plotz et al. (2003), Pizov et al. (1987)
Air leak syndromes	Pediatric and adult patients	Rescue	HFOV in these patients can have mixed results. Only in selected patients apparent clinical benefit compared to CMV has been shown	III	Markus-Rodden et al. (2008), Ha and Johnson (2004), Briggs et al. (2003), Shen et al. (2002), McGinley et al. (2001)
Acute lung injury following trauma	Adult patients	Rescue	Clinical benefit seems to be comparable with other patients with acute respiratory distress syndrome	III	Briggs et al. (2009), Funk et al. (2008), Kao et al. (2006)
Burn and smoke inhalation	Pediatric and adult patients	Rescue	HFOV seems beneficial in patients with only burn but no inhalation injury	III	Jackson et al. (2002), Cartotto et al. (2009), Cartotto (2009)
Acute respiratory distress with brain trauma	Pediatric and adult patients	Rescue	Raised intracranial pressure does not present an absolute contraindication in selected patients with concomitant lung injury	III	Lo et al. (2008), Bennett et al. (2007)
Acute chest syndrome	Pediatric patients	Rescue	Refractory hypoxemia on CMV can be improved with HFOV	III	Wratney et al. (2004)

Levels of evidence were graded according to an adaptation of the Preventive Services Task Force. Guide to clinical preventive services: report of the USA (Preventive Services Task Force 1996). *I-A* evidence obtained from a systematic review of at least two properly conducted randomized controlled trials, *I-B* evidence obtained from at least one properly randomized controlled trial, *II-1* evidence obtained from well-designed controlled trials without randomization, *II-2* evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group, *II-3* evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence, *III* opinions of respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees

The focus in very preterm patients has been on the elective use of HFOV ventilation. Premature neonates most at risk for chronic lung disease have been included in studies comparing HFOV and CMV as first choice. Although data suggest significant benefits in pulmonary outcomes when HFOV is applied with a recruitment strategy in preterm infants with respiratory distress syndrome, when compared with CMV, it is still not clear whether HFOV is really superior in terms of overall outcome in this population, as careful CMV may allow investigators to achieve similar outcome data (Bollen et al. 2003). Two large multicenter trials that emphasized alveolar recruitment as part of the strategy in HFOV dominate current evidence (Courtney et al. 2002; Johnson et al. 2002). The US trial used a strategy in the CMV group that targeted a tidal volume of 5–6 mL/kg of body weight. This study showed a statistically nonsignificant reduction in days on the ventilator (13 days in the HFOV group vs. 21 days in the CMV group) and a significant decrease in the need for supplemental oxygen at 36 weeks of gestational age in favor of HFOV (Courtney et al. 2002). The other trial, the UK Oscillation Study, utilizing not as vigorously controlling ventilator protocols, could show no difference in outcome between the two study arms (Johnson et al. 2002).

Low gestational age or birth weight, intra-uterine growth restriction, severity of lung disease, and exposure to perinatal inflammation are considered important risk factors (Egretau et al. 2001). Differences in these risk factors result in different risk profiles for chronic lung disease. This could explain inconsistency in occurrence of chronic lung disease between trials, as inclusion of infants with a very low or a very high a priori risk for chronic lung disease may override any treatment effect of the ventilation strategy if not compensated by an adequate sample size (van Kaam and Rimensberger 2007).

19.1.1.6.1.2 Long-Term Outcome

Neuromotor outcome has been of concern in HFOV, as one of the first trials reported increased

risk of intraventricular hemorrhage and periventricular leukomalacia associated with HFOV (The HIFI Study Group 1989). However, this trial was criticized because the methodology used to apply HFOV did not include methods to recruit lung volume (Bryan and Froese 1991). Moreover, in a trial which initially demonstrated a higher incidence of intraventricular hemorrhage in HFOV-treated neonates, at 2 years of follow-up, neuromotor outcome was comparable to CMV (Truffert et al. 2007). Furthermore, neurodevelopmental outcome was studied in children that entered into the UK Oscillation Study, which was designed to evaluate these outcomes (Johnson et al. 2002). The prevalence of severe neurodevelopmental disability was similar in children who received HFOV or CMV (relative risk 0.93, 95 % confidence interval 0.74–1.16) (Marlow et al. 2006). Long-term pulmonary function, frequency of hospitalization, or disabilities were not found to differ among children treated with HFOV or CMV either (Gerstmann et al. 2001; Thomas et al. 2004).

19.1.1.6.1.3 Recommendation

HFOV as a first-line therapy of respiratory distress in premature neonates does not offer convincing benefits compared to CMV to be accepted as a sole treatment option for these patients. Application of ventilation strategy is likely to be more important than type of ventilator. However, carefully applied CMV can only yield comparable results with HFOV as long as the targets of lung protective ventilation can be met. Failure to recruit the lungs, to limit tidal volumes, or to accept hypercapnia can prompt for the use of HFOV as an alternative therapy. On the other hand, carbon dioxide levels and hemodynamic parameters have to be carefully monitored, and a high lung volume strategy should be employed when using HFOV, to avoid neurological damage.

19.1.1.6.2 Rescue HFOV in Respiratory Distress Syndrome

Timing of initiating of HFOV has been considered to be an important factor. Animal experiments have demonstrated that only a few breaths

during CMV could suffice to trigger the cascade of ventilator-induced lung injury (Bjorklund et al. 1997). Delayed start of HFOV could, therefore, attenuate potency for beneficial effects (van Kaam and Rimensberger 2007). Rescue use of HFOV in preterm infants is only described in one trial. This trial was performed in the pre-surfactant era, limiting interpretation of results (HiFO Study Group 1993; Bhuta and Henderson-Smart 2000). Early rescue use of HFOV has been studied in nearly term and term infants. Neonates with gestational age >34 weeks were managed with HFOV if they required fractional inspired oxygen above 0.5 with mean airway pressure above 10 cm H₂O. Seventy-seven children fulfilled these criteria of which 70 (91 %) could be successfully weaned from HFOV (Ben et al. 2006a). A Cochrane review of the rescue use of HFOV in newborns more than 34 weeks gestation found only one randomized controlled study. This rescue trial of 79 infants (58 % met ECMO criteria), conducted by Clark et al., showed improvement in gas exchange in 63 % of the patients in whom CMV failed, whereas use of CMV, after failure of HFOV, was not effective (Clark et al. 1994). There were no significant differences in the numbers of patients requiring ECMO, days on a ventilator, days on oxygen, or days in the hospital between the two groups.

19.1.1.6.2.1 Recommendation

Rescue use of HFOV after CMV failure is indicated to improve short-term improvements of gas exchange. However, there is no convincing evidence to recommend HFOV to improve long-term outcome. It could be argued that once CMV has failed, prognosis cannot be enhanced by HFOV and, therefore, HFOV should be initiated earlier.

19.1.1.6.3 HFOV for Other Indications

Randomized trials that studied HFOV in neonates included mostly patients with respiratory distress syndrome. The efficacy of HFOV to attenuate ventilator-induced lung injury in other causes of respiratory failure, therefore, for the larger part remains to be investigated.

19.1.1.6.3.1 Severe Pulmonary Dysfunction and Intractable Respiratory Failure

Two trials have studied the use of HFOV compared to CMV in term or near-term infants with severe pulmonary dysfunction (Henderson-Smart et al. 2009). One trial, involving “elective” use of HFOV, randomized 118 infants at the start of CMV (Rojas et al. 2005). The other trial of “rescue” HFOV randomized 81 infants with respiratory failure already on CMV (Clark et al. 1994). Neither trial showed evidence of a reduction in mortality at 28 days or in failed therapy on the assigned mode of ventilation requiring crossover to the other mode. Neither study reported significant differences in the risk of pulmonary air leak, chronic lung disease (28 days or more on oxygen), or intracranial injury.

19.1.1.6.3.2 Recommendation

There is no convincing evidence to support the use of HFOV in neonates with severe pulmonary dysfunction or intractable respiratory failure. However, evidence is scarce and more research is needed to identify patients that might benefit from HFOV.

19.1.1.6.3.3 Diaphragmatic Hernia

Several descriptive studies report outcome of HFOV in neonates with diaphragmatic hernia (Datin-Dorriere et al. 2008; Migliazza et al. 2007). In a retrospective study neonatal outcome of isolated congenital diaphragmatic hernia treated with early HFOV and delayed surgery was analyzed. Survival rate at 1 month was 65.9 % (Datin-Dorriere et al. 2008). Migliazza et al. described a similar experience adopting a “gentle ventilation” strategy, using HFOV, of 111 infants with congenital diaphragmatic hernia (Migliazza et al. 2007). The overall survival rate was 69.4 %, comparable to Datin-Dorriere et al.

19.1.1.6.3.4 Recommendation

Evidence of HFOV in diaphragmatic hernia is restricted to descriptive studies. This establishes HFOV as a feasible treatment option but not as the recommended therapy in this group of patients.

19.1.1.6.3.5 Severe Persistent Pulmonary Hypertension

In a randomized multicenter trial, the use of HFOV combined with nitric oxide in severe persistent pulmonary hypertension of the newborn has been investigated (Kinsella et al. 1997a). In this study, the combination of HFOV with nitric oxide was more beneficial than nitric oxide with CMV or HFOV alone. However, treatment success was defined as response rate and differences in clinical relevant outcomes, or prevention of extracorporeal membrane oxygenation could not be assessed by design of the trial.

19.1.1.6.3.6 Recommendation

Although HFOV seems a viable treatment option for treatment failure of CMV combined with inhaled nitric oxide, there is no definitive evidence that HFOV is more effective in preventing extracorporeal membrane oxygenation or improving clinical outcome than CMV combined with inhaled nitric oxide.

19.1.1.7 HFOV in the Pediatric Intensive Care Unit

In pediatric intensive care unit patients, there is less evidence to direct selection of HFOV. Evidence has to be translated from studies performed in neonatal or adult patients. In only one randomized trial HFOV has been compared to CMV in pediatric patients with acute respiratory distress syndrome (Arnold et al. 1994). No randomized trials have been performed that looked at the elective use of HFOV compared to CMV. Yet, use of HFOV has become ingrained in pediatric practice and is used frequently in children with acute respiratory distress syndrome, despite the lack of evidence to support this (Randolph et al. 2003).

19.1.1.7.1 HFOV in Acute Respiratory Distress Syndrome

The first description of acute respiratory distress syndrome originates from Ashbaugh describing 12 patients with acute respiratory distress, cyanosis refractory to oxygen therapy, decreased lung compliance, and diffuse infiltrates evident on chest X-ray (Ashbaugh et al. 1967). According to a prospective cohort study, the prevalence of

acute respiratory distress syndrome or acute lung injury is about 9 % among adult intensive care patients and 39.6 % among ventilated patients (Roupie et al. 1999). In pediatric patients, acute respiratory distress is a more rare syndrome with incidences ranging from 1.4 to 7.9 % (Yu et al. 2009; Dahlem et al. 2003). Mortality, however, is high ranging from 31.4 to 61 %, particularly when compared to normal PICU mortality. A hallmark feature of acute respiratory distress syndrome is low compliance, necessitating high pressures to maintain sufficient tidal volume. Tidal volume, which is large relative to lung compliance, may lead to alveolar rupture and radiological evidence of extra-alveolar air. Distribution of tidal volume to the high-compliance regions causes stretching and sheer forces on the alveolar wall (Dreyfuss and Saumon 1998; Parker et al. 1993). When parts of the lung are consolidated, e.g., not recruitable, a “normal” tidal volume may still lead to overstretching of remaining alveoli, increasing already existent lung disease in acute respiratory distress syndrome.

19.1.1.7.1.1 HFOV for Acute Respiratory Distress Syndrome in Pediatric Patients

One crossover trial comparing rescue HFOV with CMV in pediatric acute lung injury and acute respiratory distress syndrome showed that HFOV was associated with higher mean airway pressures, improved oxygenation, and a reduced need for supplemental oxygen at 30 days (Arnold et al. 1994). In a prospective clinical study, HFOV in 20 pediatric patients with acute respiratory failure due to a variety of causes showed improvement of gas exchange in a rapid and sustained fashion (Ben et al. 2006b).

19.1.1.7.1.2 HFOV for Acute Respiratory Distress Syndrome in Adult Patients

The use of HFOV in the context of acute respiratory distress syndrome in adult patients has been studied in 4 randomized trials (Derdak et al. 2002; Bollen et al. 2005; Young et al. 2013; Ferguson et al. 2013). In the first trial of 148 patients there was a nonsignificant lower 30-day mortality in the HFOV group (37 % vs. 54 %, $p=0.10$). However, the CMV protocol did not use

the current standard for volume- and pressure-limited lung protective ventilation, and the study was not powered to detect mortality differences since mortality was only a secondary outcome criteria (Derdak et al. 2002). A second trial of 61 acute respiratory distress syndrome patients comparing HFOV with CMV also revealed no significant differences in survival without supplemental oxygen or ventilation support (32 % vs. 38 %, adjusted odds ratio 0.80, 95 % confidence interval 0.22–2.97, $p=.79$) (Bollen et al. 2005). A post hoc analysis suggested that patients with the most severe hypoxemia had a trend toward a benefit from HFOV. In contrast, recently two large RCTs comparing HFOV with a conventional lung protective ventilation, the Oscillation in ARDS (OSCAR) (Young et al. 2013) and the Oscillation for Acute Respiratory Distress Syndrome Treated Early (OSCILLATE) (Ferguson et al. 2013) trials, showed either no benefit (for the OSCAR trial) or even harm (for the OSCILLATE trial) with HFOV in adults with early moderate-to severe ARDS. The OSCILLATE trial has been stopped after 548 patients (planned 1200) on the recommendation of the data monitoring committee because of an unexpected high in-hospital mortality of 47% in the HFOV group, as compared with 35% in the control group (relative risk of death with HFOV, 1.33; 95% confidence interval, 1.09 to 1.64; $p=.005$). In this trial the patients randomized to HFOV received more sedation ($p<.001$), neuromuscular blockers ($p<.001$), and vasoactive drugs ($p=.01$) than those randomized to CMV. This latter suggests that the recruitment protocol and the high volume strategy with reported mean airway pressures of more than 30 cmH₂O during HFOV after recruitment might have caused lung overdistention and hemodynamic compromise, which might explain the high 30-day mortality. For this reason this trial has been criticized repeatedly (Malhorta and Drazen 2013; Liaudet 2013; Guervilly et al. 2013).

19.1.1.7.1.3 Acute Respiratory Distress Syndrome, Timing of HFOV

The use of HFOV is considered to be a safe alternative to CMV in adult patients with severe acute respiratory distress syndrome who have failed CMV (Chan and Stewart 2005). Immediate use

Table 19.2 Recommendations to initiate HFOV in acute respiratory distress syndrome

Indications	References
1 An apparent oxygenation failure using CMV, i.e., the need for an $\text{FiO}_2 > 0.60$, despite optimizing PEEP, inverse ratio ventilation, or other conservative measures to improve oxygenation such as adequate circulatory support High inspiratory pressures needed to maintain adequate oxygenation or resulting tidal ventilation volumes in CMV that are too small to result in sufficient carbon dioxide elimination, resulting in respiratory acidosis (i.e., $\text{pH} < 7.20\text{--}7.25$)	
2 Oxygenation failure: $\text{FiO}_2 \geq 0.7$ and positive end-expiratory pressure > 14 cm H ₂ O Ventilation failure: $\text{pH} < 7.25$ with tidal volume ≥ 6 mL/kg predicted body weight and plateau airway pressure ≥ 30 cm H ₂ O	Fessler et al. (2007)
3 $\text{FiO}_2 > 0.60$ and $\text{SpO}_2 < 88\%$ on conventional ventilation with positive end-expiratory pressure > 15 cm H ₂ O Plateau pressures > 30 cm H ₂ O Mean airway pressure > 24 cm H ₂ O Airway pressure release ventilation high pressure 35 cm H ₂ O	Higgins et al. (2005)

of high-frequency ventilation in patients with acute respiratory distress syndrome has been advocated (Goutorbe et al. 2008). However, further research is needed to determine the ideal patients, timing, and optimal technique with which to provide HFOV.

Oxygenation failure has been classically an indication for HFOV. Oxygenation failure requires a ventilation strategy in which positive end-expiratory pressure is raised to limit fractional inspired oxygen while at the same time peak inspiratory pressures and tidal volumes have to be limited as well. Table 19.2 summarizes the criteria reported in literature to initiate HFOV in oxygenation failure.

The oxygenation index has been proposed as a candidate marker to determine the timing of transition of CMV to HFOV in case of oxygenation failure (Bollen et al. 2005; van Genderingen et al. 2002). The oxygenation index combines the most important characteristics of oxygenation failure

and can be regarded as a cost-benefit indicator. The cost being fractional inspired oxygen and mean airway pressure and the arterial oxygen content as a measure of the benefit obtained. An oxygenation index above 20 could serve as a marking point to initiate HFOV in acute respiratory distress syndrome or intractable oxygenation failure.

19.1.1.7.1.4 Recommendation

There is no evidence that HFOV offers a clear clinical benefit over CMV (Wunsch and Mapstone 2004). However, in selected patients, HFOV could be indicated. Proposals for indications are listed in Table 19.2, but evidence to back up these protocols is still missing. Further research is needed to establish the position of HFOV as a second-line treatment in acute respiratory distress syndrome.

19.1.1.7.2 HFOV for Other Indications

Evidence of indications for HFOV other than acute respiratory distress syndrome is largely anecdotal. In these patient groups no randomized or controlled trials have been performed.

19.1.1.7.2.1 Small Airway Disease

In small airway disease adequate carbon dioxide removal is of prime concern. Carbon dioxide elimination is directly correlated with expiratory minute volume in CMV. HFOV, however, does not directly rely on tidal volume movement, but can be very efficient in carbon dioxide removal through alternative mechanisms. Airway obstruction and plugging in HFOV on the other hand can severely hamper carbon dioxide elimination. Use of HFOV in small airway disease has been suggested in patients in which higher mean airway pressure can stent the airways, preventing them from collapsing (Duval and van Vught 2000; Duval et al. 2000). The continuous distending airway pressure of HFOV can be used to open up and stent the small airways (“open-airway” concept in analogy to the “open-lung” concept).

HFOV has been used to treat respiratory failure due to RSV bronchiolitis (Berner et al. 2008). The proportion of infants with RSV infection requiring CMV is reported to vary around 25 % of those infants that are admitted to the intensive

care unit (Larrar et al. 2006; Campion et al. 2006). Adequate mechanical ventilation in obstructive lung disease represents a challenge. High peak inspiratory pressures are needed to guarantee sufficient tidal volumes and minute ventilation (Leclerc et al. 2001). The use of HFOV has been described as rescue intervention in several cases to improve severe hypoxemic respiratory failure while carbon dioxide elimination was compromised (Kneyber et al. 2005; Thompson et al. 1995; Medbo et al. 1997; Duval et al. 1999). These reports show that respiratory failure with hypercapnia can be managed with HFOV using high mean airway pressure and large pressure swings while preserving spontaneous breathing. Use of HFOV in an infant with cystic fibrosis and viral bronchiolitis has been described as well. Severe hypercarbic respiratory failure was treated successfully with HFOV in this patient (Seferian et al. 2006).

The “open-airway” concept as an approach to ventilate patients with small airway disease is further described by Slee-Wijffels et al. in 17 patients along with 32 patients with diffuse alveolar disease (Slee-Wijffels et al. 2005). The latter group was characterized by oxygenation failure and a considerably higher mortality compared to patients with small airway disease. Using the “open-airway” concept HFOV was effective in achieving adequate ventilation in all of these patients.

Management of status asthmaticus has been described in a case report (Duval and van Vught 2000). It was suggested that obstructive airway disease could be safely managed, providing certain conditions are met: application of sufficiently high mean airway pressures to open and stent the airways (“an open-airway strategy”), lower frequencies to overcome the greater attenuation of the oscillatory waves, permissive hypercapnia, and longer expiratory times and muscle paralysis to avoid spontaneous breathing.

19.1.1.7.2.2 Recommendation

The use of HFOV in pulmonary conditions with increased airway resistance and prolonged time constants, such as small airway disease, remains controversial. Use of HFOV in these patient groups is anecdotal. Therefore, treatment of small airway disease with HFOV should be

restricted to centers with extensive experience with HFOV and to those patients in whom conventional treatment options fail.

19.1.1.7.2.3 Asymmetric Lung Injury

HFOV has been used to selectively ventilate the collapsed lung in patients with asymmetric acute lung injury, while the more homogeneously infiltrated lung was managed by conventional ventilation (Terragni et al. 2005). The same strategy in asymmetric pulmonary disease has been described by Plotz et al. in a 14-year-old patient (Plotz et al. 2003). The first report on this particular use of HFOV was published by Pizov in the management of traumatic tear of bronchus in a child (Pizov et al. 1987). The rationale behind this treatment is that HFOV can thus be used to selectively apply a high mean airway pressure to the consolidated lung without creating alveolar overdistension and volutrauma in the relatively disease-free opposite lung.

19.1.1.7.2.4 Recommendation

This usage of HFOV should be considered experimental and should only be reserved for the very special cases in centers with experience in HFOV.

19.1.1.7.2.5 Air Leak Syndromes

HFOV in air leak syndromes can have mixed results. On the one hand, HFOV does not necessitate pressure swings as experienced in CMV. This could have a beneficial effect on the causative lesions of the air leak syndrome. On the other hand, higher mean airway pressure in HFOV can be hypothesized to maintain the air leak. Only case reports of the use of HFOV specifically in air leak syndromes have been published (Galvin et al. 2004). HFOV has been used in traumatic tracheal laceration in a pediatric patient (Markus-Rodden et al. 2008). HFOV was initiated in this case because of concomitant lung injury resulting in deteriorating respiratory status. Another case report describes the successful use of HFOV in a high output bronchopleural fistula (Ha and Johnson 2004). A case of Lemierre disease in a 14-year-old girl resulting in cavitating pneumonia was managed by a combined therapy of nitric oxide and HFOV (Briggs et al. 2003). A case report describes the use

of HFOV to manage pneumatoceles. It was argued that CMV could lead to distension of the pneumatoceles through air-valve mechanisms (Shen et al. 2002). HFOV using a permissive hypercapnia and hypoxemia strategy has also been used in pediatric acute respiratory distress syndrome with pneumomediastinum (McGinley et al. 2001).

19.1.1.7.2.6 Recommendation

HFOV cannot be recommended as a first-line therapy as only anecdotal reports describe its use in these patients. If HFOV is used, fractional inspired oxygen should be increased in favor of airway pressure.

19.1.1.7.2.7 Acute Lung Injury Following Trauma

Use of HFOV has been studied as a rescue therapy for adult trauma patients (Briggs et al. 2009). This retrospective study of 24 patients concluded that although HFOV improved oxygenation, severity of traumatic injury and organ failure were predictors of survival, not respiratory status. In trauma patients with severe pulmonary contusion, HFOV has been used as rescue therapy (Funk et al. 2008). Rapid improvement in oxygenation index and $\text{PaO}_2/\text{FiO}_2$ ratio was achieved. HFOV in surgical patients appeared to be safe and effective in correcting oxygenation failure in 16 patients that failed on CMV (Kao et al. 2006). A considerable increase in $\text{PaO}_2/\text{FiO}_2$ ratio was observed that was maintained throughout the study after initiation of HFOV.

19.1.1.7.2.8 Recommendation

Not surprisingly, HFOV to treat lung injury after trauma shows comparable results to HFOV in treatment of acute respiratory distress syndrome. However, evidence in these patients is anecdotal and does not seem to represent a group different from other patients with acute lung injury or acute respiratory distress syndrome.

19.1.1.7.2.9 Burn and Smoke Inhalation Patients

The associated risk of mortality in acute lung injury due to smoke inhalation has been reported as high as 40–50 %. Mortality may be due directly to respiratory failure and inability to oxygenate

sufficiently, or it may result from associated multisystem organ failure or ventilator-associated pneumonia. Accepting hypercapnia when using low tidal volumes to prevent ventilator-induced lung injury, permissive hypercapnia, has been shown to be safe to a modest degree in these patients (Hickling et al. 1994; Laffey et al. 2004; Bidani et al. 1994). However, very little has been reported on the use of HFOV after inhalation injury, aside from one animal experiment (Cioffi et al. 1993), a pediatric case report (Jackson et al. 2002), and data from 19 adult burn and inhalation injury patients treated with HFOV (Cartotto et al. 2009; Cartotto 2009). The unique clinical and pathophysiologic features of smoke inhalation could pose limitations to the application of HFOV. Acute respiratory distress syndrome in smoke inhalation injury could be a more heterogeneous disease resulting in non-recruitable alveoli thereby limiting the beneficial effects of high-frequency ventilation by opening and recruiting alveoli (Crotti et al. 2001; Gattinoni et al. 2006). Patients with burns and smoke inhalation were found to respond less vigorously to HFOV as those with burn injury alone. Those with inhalation injury failed to achieve significant improvement in $\text{PaO}_2/\text{FiO}_2$ ratio or oxygenation index compared with baseline on CMV before HFOV and never obtained a significant reduction in oxygenation index (Cartotto et al. 2009). This contrasted sharply with non-inhalation cases where there was a significant improvement in oxygenation within 8 h of HFOV.

19.1.1.7.2.10 Recommendation

Based on limited evidence, HFOV cannot be recommended to treat isolated inhalation injury. Only in burn patients with acute respiratory distress syndrome, HFOV could have beneficial effects.

19.1.1.7.2.11 Acute Lung Injury with Concurrent Brain Injury

Modern management of acute traumatic brain injury in children aims to minimize secondary physiologic insults such as raised intracranial pressure, reduced cerebral perfusion pressure, and hypotension or hypoxemia by optimizing

cerebral perfusion and oxygenation while the brain recovers (Jones et al. 2003). CMV is used routinely in these patients to prevent hypercapnia and hypoxia during the acute phase. Effective gas exchange, however, can be problematic in those with coexisting lung pathology. Lung protective ventilation strategies used in CMV could conflict with therapeutic goals in treatment of traumatic brain injury. HFOV in these children has raised concerns about the potential adverse effects on the cerebral venous drainage and intracranial pressure. In a case report of two head-injured children, HFOV was used to handle concomitant traumatic lung injury. In both these patients, a dramatic reduction in intracranial pressure was observed soon after the use of HFOV (Lo et al. 2008). A comparable case series of five patients reached the same conclusion that HFOV appeared to be a relatively safe and effective means of oxygenating patients with severe acute respiratory distress syndrome and concomitant increased intracranial pressure due to acute brain injury (Bennett et al. 2007). HFOV appeared a safe rescue treatment in head-injured patients in a case series of five adult patients with severe respiratory insufficiency as well (David et al. 2005).

19.1.1.7.2.12 Recommendation

Raised intracranial pressure, classically considered a contraindication for HFOV, does not seem an absolute contraindication in patients with concomitant respiratory failure. In these patients, when intracranial pressure is monitored, HFOV can be an alternative to CMV.

19.1.1.7.2.13 Acute Chest Syndrome

Severe acute chest syndrome can cause hypoxemia refractory to conventional treatment. Obstructive mucus plugging and the development of acute respiratory distress syndrome may underlie the pathophysiology of refractory hypoxemia in acute chest syndrome. In disease processes with high airway resistance and obstructive mucus plugging, HFOV may predispose to air trapping and increased morbidity secondary to air leak syndromes. A case series of six pediatric patients describe the successful treatment of acute chest syndrome found in

sickle cell anemia (Wratney et al. 2004). Patients failing CMV could be safely managed by HFOV, without strong concern about impaired secretion clearance or air leak syndromes.

Future Perspectives

- In neonatal patients, the tendency is strongly in favor of avoiding invasive ventilation. Once invasive ventilation is inevitable, baseline risk of chronic lung disease could determine whether or not HFOV could have clinical benefits over CMV. Heterogeneity among trials that studied the elective use of HFOV could be explained by differences in baseline risk of chronic lung disease. However, CMV with careful lung protective ventilation strategy seems to yield comparable results.
- In pediatric patients it is not to be expected that HFOV will replace CMV as the first-choice mode of mechanical ventilation. Indications for HFOV transpire when lung protective ventilation strategies are no longer feasible using CMV. Indications for HFOV could depend more on respiratory-dependent predictors of ventilator-induced lung injury than on specific disorders, like acute respiratory distress syndrome. High fractional oxygen requirement combined with raised mean airway pressures as reflected by the oxygenation index could be used to identify patients most at risk of ventilator-induced lung injury and thus could indicate when to apply HFOV.
- Individual patients with varying lung pathology and heterogeneous disease patterns will require individual assessment of which ventilation settings will be most optimal. Conditional on those factors it should be determined whether or not HFOV offers benefits over CMV. Unfortunately, convincing evidence to guide these decisions is still missing.

19.1.1.7.2.14 Recommendation

Acute chest syndrome can be managed by HFOV. However, the evidence is anecdotal and only shows the feasibility of using HFOV in these patients.

Essentials to Remember

- There are no strict, absolute indications to use HFOV in favor of CMV. Moreover, the use of HFOV should not be regarded as the key to improve outcome but as a means to enable lung protective ventilation. Only when lung protective ventilation is not feasible using CMV, HFOV could outperform CMV. Whether or not lung protective ventilation is possible and how this will change the prognosis with respect to ventilator-induced lung injury is determined by patient and disease characteristics.
- The general aim of lung protective ventilation is to avoid overdistension on the one hand and atelectasis on the other hand. This can be visualized as a “safe window” on the pressure-volume curve. The size of this safe window can be translated to tidal volume. Thus, the smaller the safe window, the smaller the tidal volumes should be. In this respect, HFOV provides the theoretically most optimal ventilation mode. However, at present there are no conclusive studies that identify those specific patients.
- The relatively high distending airway pressure, possible with HFOV, has been taken advantage of to “stent” the airway in small airway disease. However, evidence of the effectiveness for this indication is anecdotal, as is the evidence for use in air leak syndromes that uses HFOV with a relatively low mean airway pressure. In the latter it is thought that the absence of large pressure swings, in CMV, prevents maintaining air leak.

19.1.2 Indications for High-Frequency Jet Ventilation (HFJV)

Martin Keszler

Educational Aims

- Describe the experimental evidence in support of specific clinical applications of HFJV.
- Describe the clinical evidence in support of specific clinical applications of HFJV.
- Indicate the limitations of available studies and their applicability to today's patient population.

During the 1980s and 1990s, HFJV became firmly established as an important therapeutic alternative, based primarily on its effectiveness in treating air leak. However, despite more than 20 years of laboratory and clinical research with dozens of peer-reviewed publications, the exact role of HFJV (and other high-frequency ventilation techniques) remains controversial with no clear consensus emerging. At one end of the spectrum, a minority of clinicians use HFJV as a

first-line mode of ventilation for extremely low-birth-weight infants they believe to be at high risk of chronic lung disease, while at the other extreme are those who view it strictly as a rescue technique, to be used only when conventional ventilation has clearly failed. Majority of clinicians appear to have a more measured approach, utilizing HFJV as an early rescue mode in infants who are judged to be at high risk of complications with conventional ventilation because they require high inspiratory pressure or have developed air leak complications, even though they are still maintaining adequate gas exchange on conventional ventilation.

The ongoing controversy regarding indications for HFV in general and HFJV in particular is related to the conflicting results of published clinical trials and the recognition that therapeutic options such as surfactant replacement therapy and synchronized, volume-targeted ventilation, which were not available when the early studies of HFV were conducted, limit the applicability of the conclusions to today's neonatal patients. However, several well-supported indications do exist. In the following paragraphs I will briefly review available literature on HFJV in various disease processes and formulate evidence-based recommendations for the use of HFJV (Table 19.3).

Table 19.3 Proposed indications for HFJV

1	Air leak syndromes	Level 1 evidence for PIE Level 3 evidence for BPF and TEF
2	Severe uniform disease (RDS) Rescue therapy	Level 3 evidence (cohort and historical control studies)
3	Severe uniform disease (RDS) First-line treatment	Level 1 evidence of effect, but no clear recommend from systematic review
4	Severe nonuniform disease (e.g., aspiration syndromes)	Level 4–5 strong uncontrolled and anecdotal evidence, small RCT showed strong trend
5	Pulmonary hypoplasia (e.g., congenital diaphragmatic hernia)	Level 4–5, but physiologically sound
6	Severe chest wall restriction and/or upward pressure on the diaphragm due to abdominal distension	Level 3 evidence (cohort studies, supported by animal research)
7	Severe respiratory failure and PPHN (ECMO and iNO candidates)	Level 4–5 strong uncontrolled and anecdotal evidence, small RCT showed strong trend
8	Impaired hemodynamic status	Level 3 evidence
9	Nonuniform disease – BPD	Level 4 evidence (small cohort studies)
10	Intraoperative use	Level 4–5

The strength of the recommendation is indicated using the “level of evidence” scheme proposed by the Oxford University Centre for Evidence-Based Medicine (<http://www.cebm.net/index.aspx?o=1025>)

19.1.2.1 Respiratory Distress Syndrome and Other Surfactant Deficiency States

There are sound pathophysiologic reasons why patients with respiratory distress syndrome (RDS) and congenital pneumonia may benefit from high-frequency jet ventilation. Their lungs are prone to atelectasis and the time constants are short, thus lending themselves well to ventilation at high frequencies with little risk of air trapping. The lungs are relatively uniformly involved and can be effectively recruited (made more homogeneously inflated) with appropriate lung recruitment strategies. The rationale behind all HFV modes is that the use of small tidal volumes at high frequencies allows more uniform lung inflation and causes less damage to severely noncompliant lungs than do the larger tidal volumes of conventional ventilation. While more extensive animal data are available for HFOV, there are several animal studies that document less lung injury with HFJV, compared to conventional ventilation (Keszler et al. 1982; Quan et al. 1984; Sugiura et al. 1990), as well as the ability to use lower airway pressures (Boros et al. 1989).

19.1.2.1.1 Clinical Studies: Rescue Therapy

As with most new therapies, HFJV in the clinical setting was initially used in late rescue mode. Although many of the early studies included infants whose lung disease was complicated by air leak (discussed in detail later in the chapter), their underlying disease was severe uniform atelectatic disease, mostly RDS. Those early studies demonstrated apparent benefits with improved gas exchange and better survival in these moribund infants, relative to expectations (Boros et al. 1985; Spitzer et al. 1989). Subsequently, Baumgart et al. described a series of potential candidates for extracorporeal membrane oxygenation (ECMO) who were treated with HFJV also with apparently encouraging results (Baumgart et al. 1992). Infants with homogeneous lung disease (RDS or pneumonia) responded much better than those with meconium aspiration or lung hypoplasia. A small randomized trial by Carlo et al. failed to confirm improved survival (Carlo et al. 1990). The investigators used a device that

is not commercially available and a low-pressure strategy. The study employed a sequential analysis design and was only powered to detect extreme improvement in survival from 15 to 85 %. Davis et al. suggested that the combination of HFJV and exogenous surfactant may be more effective than either technique alone, based on a series of 28 infants with poor initial response to exogenous surfactant (Davis et al. 1992).

Despite the lack of well-controlled clinical trials, many clinicians continue to use HFJV in rescue mode, based on available literature and personal experience (the response to HFJV is often quite dramatic and unequivocal). The time for controlled clinical trials of rescue HFJV has passed, lack of level 1 evidence notwithstanding, high-frequency ventilation has become a de facto standard of care in infants with severe RDS failing conventional ventilation, in part because lung volume recruitment is more easily achieved with high-frequency ventilation. The trend has shifted over time from late rescue to early rescue, as discussed above. Today, most clinicians will initiate HFJV long before the infant is in extremis, using high inflation pressure requirement or CO₂ retention as the criteria for HFJV.

19.1.2.1.2 Clinical Studies: First-Line Treatment

Two large randomized trials of HFJV in uncomplicated RDS were conducted concurrently in the mid-1990s and came to diametrically opposite conclusions. The smaller single-center study by Wiswell et al. failed to show any pulmonary benefit but instead showed a disturbing increase in the combined endpoint of death, severe IVH or PVL (Wiswell et al. 1996a). The mean birth weight was 954 g with gestational age of <27 weeks. Only 20 % of infants received antenatal steroids, and the mean age at randomization was 7 h. Severe intracranial hemorrhage occurred in 22 % of the control group compared to 41 % of HFJV infants; cystic periventricular leukomalacia (PVL) occurred in 6 % of control infants and 31 % of HFJV infants. The study was stopped by its Data Safety Monitoring Committee because of the high incidence of complications. The adverse neuroimaging findings in the HFJV

infants were subsequently traced back to inadvertent hyperventilation (Wiswell et al. 1996b) that resulted from the use of low PEEP and consequent marginal oxygenation, preventing clinicians from further lowering PIP despite uncomfortably low PaCO₂ values.

Concurrently, we studied 130 infants <1,500 g who had significant RDS despite surfactant therapy in a multicenter randomized clinical trial. Mean birth weight was 1,020 g and mean gestational age 27.3 weeks with mean age at randomization of 8 h, all virtually identical to the single-center study. In contrast to the Wiswell study, we found a reduction in chronic lung disease at 36 weeks corrected age (20 % vs. 40 %, $p=0.037$, odds ratio=0.37, 95 % CI=0.14–0.94) and less need for home oxygen therapy (5.5 % vs. 23.1 %, $p=0.019$, odds ratio 0.19, 95 % CI=0.04–0.84) in infants treated with HFJV (Keszler et al. 1997). There was no increase in complications, including severe IVH/PVL (27.6 % for conventional ventilation vs. 19.7 % for HFJV).

How can the findings of these two studies be reconciled? They were done concurrently and under a very similar protocol and used an identical high-frequency ventilator. There appeared to be only one key difference – our multicenter trial specified an HFJV ventilator strategy aimed at optimizing lung volume, while the single-center study utilized the low-pressure strategy historically used to treat air leak syndrome. However, it turned out that not all HFJV infants in the multicenter study were treated with the prescribed optimal volume strategy; a substantial proportion of the patients were in fact ventilated using a traditional low-pressure strategy of HFJV, similar to that used in the Wiswell study. Although this protocol deviation detracted from the overall quality of the study, it provided an opportunity to compare the two strategies of HFJV. Because this is a post hoc analysis, it should be interpreted with caution, but there was a much lower incidence of IVH/PVL in the optimal volume subgroup: 9 % vs. 33 % in the low-pressure group and 28 % in the conventional group ($p<0.05$). Interestingly, once again, the low-pressure subgroup of HFJV had significantly lower PaCO₂, compared to both CV and the optimal volume HFJV subgroup.

These findings underscore the importance of using optimal ventilation strategies and point out that the skill with which a device is used is perhaps more important than the device itself.

The lingering concerns raised by the Wiswell study and the ease with which inadvertent hyperventilation occurs with HFJV are probably the main reasons why HFJV for prevention of chronic lung disease has not been adopted by a majority of clinicians, despite the fact that the Cochrane Systematic Review concluded that HFJV was associated with a reduction in BPD at 36 weeks postmenstrual age in survivors [RR 0.58 (0.34, 0.98)] with a number needed to treat of 7 (Bhuta and Henderson-Smart 1998). It is also important to realize that the infants in the two studies had much less exposure to antenatal steroids and were treated with less effective exogenous surfactant preparations than those available today. The conventional ventilation practices in the 1990s differed significantly from the way infants are ventilated today, and for all these reasons, it is clear that data from the two randomized trials cannot be directly applied today. While some clinicians feel that in their experienced hands the risks of early application of HFJV are minimal and outweighed by the benefits, this is a minority view. The Cochrane Systematic Review on the subject concluded that “until further studies ascertain the most appropriate strategy to *routinely* ventilate premature infants with HFJV safely, ventilation with HFJV cannot be recommended for preterm infants with (uncomplicated) RDS” (Bhuta and Henderson-Smart 1998).

19.1.2.2 Air Leak Syndromes

There is fairly strong consensus that HFJV is preferable to conventional ventilation (and probably to HFOV) for the treatment of severe air leak complications, such as pulmonary interstitial emphysema (PIE) and bronchopleural or tracheoesophageal fistula. This is based on sound data from animal studies (Carlson et al. 1983; Orlando et al. 1988; Ritz et al. 1984; Albelda et al. 1985) and adult patients (Turnbull et al. 1981; Rubio et al. 1986; Bishop et al. 1987; Roth et al. 1988; Poelaert et al. 1987) and on anecdotal reports of early rescue use of HFJV in infants with severe

RDS complicated by air leak (Boros et al. 1985; Spitzer et al. 1989). Boros et al. treated 10 newborn infants with refractory respiratory failure and reported that 7/9 infants with severe air leak responded to HFJV (Pokora et al. 1983). Harris and Christensen reported improvement in PIE in a majority of the 20 patients with PIE that they treated with HFJV (Harris and Christensen 1984). Gonzales et al. subsequently demonstrated a significant decrease in chest tube flow (Gonzalez et al. 1987) in infants with bronchopleural fistulae. Donn et al. (1990) and Goldberg et al. (1992) showed similar benefits in infants with tracheoesophageal fistulae. The most compelling evidence comes from the multicenter randomized controlled trial in infants with RDS complicated by PIE (Keszler et al. 1991). This was a rescue study done in the pre-surfactant era and without benefit of antenatal steroids, therefore all of the infants had severe lung disease. The major finding was that HFJV led to significantly faster and more frequent resolution of PIE. When rescue crossover of infants who were failing conventional ventilation is accounted for, survival was improved with the use of HFJV (65 % vs. 47 %, $p < 0.05$). Gas exchange was also improved significantly with HFJV, and there was a modest trend toward less BPD in the HFJV group (50 % vs. 67 %, $p = 0.17$).

Based on available data, it is recommended that any patient with significant air leak should be treated with HFJV if this device is available. There are no randomized trials of HFOV demonstrating faster or more frequent resolution of PIE. The HiFO study showed no difference in the resolution of existing air leak, although there were fewer cases of new air leak after randomization (HiFO Study Group 1993). One observational study suggested that HFOV may be able to facilitate resolution of PIE as well, but the study excluded babies that did poorly and lacked a control population (Clark et al. 1986). Oscillatory ventilation is sometimes used for air leak based on this study and by extrapolation of the HFJV data. Given the very different gas flow characteristics in the upper airway, this may not be warranted but is understandable, because HFJV is not yet available in many parts of the world.

19.1.2.3 Severe Nonuniform Lung Disease/PPHN

Several animal studies compared HFJV and conventional ventilation in animal models of meconium aspiration with some studies showing apparent advantages of HFJV and others showing no differences. These conflicting results are likely due to differences in both the ventilatory strategies and the animal models used. Mammel found no advantage of HFJV in a feline model of aspiration using HFJV at a relatively high rate immediately after instillation of meconium (Mammel et al. 1983). Ventilation and oxygenation were worse with HFJV; pulmonary artery pressures and pulmonary vascular resistance were both increased in the HFJV group. These findings are consistent with air trapping due to airway obstruction and inadequate expiratory time and would be expected immediately after aspiration of meconium. Trindade also compared IMV to HFJV with a low airway pressure strategy in a meconium aspiration model and showed no differences in gas exchange, lung mechanics, or hemodynamic variables (Trindade et al. 1985). In contrast, we studied both HFJV and HFJV combined with low-rate IMV in a juvenile canine model of meconium aspiration and found improved ventilation and oxygenation at lower mean and peak airway pressures, more so in the animals ventilated with HFJV combined with low-rate IMV (Keszler et al. 1986). There were no adverse hemodynamic effects of HFJV and no elevation of pulmonary vascular resistance was seen. In contrast to the Mammel and Trindade studies, we used a more dilute mixture of meconium, allowed the animals to stabilize for 30 min on conventional ventilation, and suctioned the trachea prior to the onset of ventilation. We used a slower HFJV rate (i.e., longer expiratory time) because of the longer time constants associated with airway obstruction. The combined HFJV animals had significantly lower histologic lung injury scores, compared to the tidal ventilation group (Keszler et al. 1988). The benefit of superimposed conventional breaths is probably the result of alveolar recruitment, made necessary by the fact that the meconium aspiration results in surfactant inactivation. Wiswell et al. investigated

the effects of four different ventilators on gas exchange and lung histology in newborn piglets and reported that animals ventilated with HFJV or with HFFI had significantly fewer histologic abnormalities than did those ventilated with conventional IMV (Wiswell et al. 1992). More recently, Wiswell compared the effects of surfactant therapy with both HFJV and CV on ventilator variables, gas exchange, and lung histology in a piglet model of MAS (Wiswell et al. 1994). Disappointingly, they were unable to demonstrate benefit of surfactant therapy or of HFJV, compared to conventional ventilation.

Taken together, these studies suggest that under some circumstances, there may be a role for HFJV in the treatment of infants with meconium aspiration syndrome (MAS). It is clear that specific clinical circumstances and the strategies used may uniquely affect the effectiveness of HFJV in this disorder. Several of the early uncontrolled series of patients with severe respiratory failure included infants with MAS and suggested possible effectiveness of HFJV as a rescue treatment in potential candidates for ECMO (Spitzer et al. 1989; Baumgart et al. 1992; Davis et al. 1992). Carlo used HFJV in infants with PPHN and reported that compared to historical controls, the HFJV infants showed lower PaCO₂ values and lower airway pressures, but oxygenation and overall outcomes were not different (Carlo et al. 1989). Only one small randomized controlled study of HFJV vs. conventional ventilation for near-ECMO patients has been published (Engle et al. 1997). HFJV improved gas exchange and showed a trend to less frequent need for ECMO. None of the 9 HFJV survivors had chronic lung disease, compared to 4 of 10 CMV infants. These differences were not statistically significant, but the study was extremely small and thus highly susceptible to type II statistical error.

Reports based on the Extracorporeal Life Support Organization Registry and data from the National Institutes of Child Health and Development Neonatal Research Network centers indicate that both HFOV and HFJV are widely used in infants with PPHN and severe uniform and nonuniform lung disease who are potential candidates for ECMO (Roy et al. 2000;

Walsh-Sukys et al. 2000). A recent paper suggests that HFJV may be more effective than HFOV in avoiding the need for ECMO: 9 % of HFJV infants vs. 44 % of HFOV infants required ECMO (Coates et al. 2008). The fact that the HFOV comparison was a historical control group and had higher baseline oxygenation index makes definitive conclusions difficult, but it appears that HFJV is at least as effective as HFOV in potential ECMO candidates. In infants with PPHN and severe lung disease, HFJV used with the optimal lung volume strategy may be helpful in optimizing lung inflation and response to iNO in the same fashion as demonstrated for HFOV by Kinsella et al. (1997b). It has been the author's practice for 25 years to use HFJV in infants with MAS with or without PPHN, more recently in combination with inhaled nitric oxide, with a response rate of over 75 % (Keszler, 2010), consistent with a recent report by Stewart et al. reporting 73 % response rate in infants with Paw >15 who were being considered for ECMO therapy (Stewart et al. 1996).

19.1.2.4 Impaired Chest Wall Movement: Abdominal Distension

Increased intra-abdominal pressure results in upward pressure on the diaphragm, reduces diaphragmatic excursion, and results in decreased compliance of the respiratory system in newborns with acute intra-abdominal disease such as necrotizing enterocolitis or postoperatively in infants with gastroschisis, omphalocele, or diaphragmatic hernia. Large tidal volume ventilation further exacerbates the hemodynamic compromise normally caused by positive-pressure ventilation, because a greater proportion of the inspiratory pressure is transmitted to the pleural space (Keszler and Abubakar 2011). Consequently, small tidal volumes and lower pressures of HFJV would be expected to offer an advantage over large tidal volume breathing. This concept was confirmed by us in an animal model of increased intra-abdominal pressure, where we demonstrated improved gas exchange, lower pressure amplitude, and better cardiac output (Keszler et al. 1993). We subsequently reported improved ventilation and hemodynamic variables

in 20 such patients when switched from conventional ventilation to HFJV (Keszler and Jennings 1997). This relatively common situation is a very clear indication for the use of HFJV. Although the published data are limited, the pathophysiologic rationale is compelling and clinical experience quite extensive.

19.1.2.5 Patients with Impaired Hemodynamic Status

A number of animal studies have examined the effects of HFJV on blood pressure and cardiac output with results that were inconsistent but in aggregate suggest improved hemodynamics in subjects with some degree of hemodynamic compromise (Otto et al. 1983; Lucking et al. 1986; Chiaranda et al. 1984), whereas no difference was seen where the hemodynamic status was good to begin with (Sugihara et al. 1987; Courtney et al. 1989). Two clinical studies specifically addressed the hemodynamic effects of HFJV in infants and young children following a variety of cardiac surgical procedures, taking advantage of the invasive hemodynamic monitoring available in these patients. Similar data are not available for newborn infants in whom direct cardiac output measurements are not available. Both studies demonstrated improved cardiac index, largely resulting from the ability of HFJV to achieve excellent gas exchange with low peak and mean airway pressures (Weiner et al. 1987; Meliones et al. 1991).

19.1.2.6 Pulmonary Hypoplasia

Although intuitively HFJV offers an advantage over CMV in infants with pulmonary hypoplasia, such as congenital diaphragmatic hernia, no randomized controlled studies exist to substantiate this impression. There is a good deal of anecdotal evidence for improved gas exchange with both HFOV and HFJV in such infants, including the early rescue trials. A recent report showed an encouraging 75 % survival rate in CDH patients ventilated with HFJV, not statistically different from the predicted survival of 63 % (Kuluz et al. 2010). Clearly, it is reasonable to assume that the ideal method of ventilating these small lungs is with a high-frequency device that maintains ade-

quate gas exchange while using very small tidal volumes. We recently demonstrated that the VT needed to achieve acceptable PaCO₂ with conventional ventilation in infants with CDH is no different from infants with uniform lung disease without hypoplasia (Sharma et al. 2010). The implication is that given the substantially reduced number of alveoli in infants with CDH, each alveolus is being stretched to a greater degree, leading to volutrauma. This conclusion provides further rationale for the use of HFV. Anecdotally, most tertiary centers where HFJV is available routinely use this therapy as first-line treatment in infants with pulmonary hypoplasia.

19.1.2.7 Bronchopulmonary Dysplasia

Traditional thinking is that high airway resistance with the resulting prolonged time constants is a contraindication to HFJV, but there is a growing number of anecdotal reports and several small, uncontrolled series of patients, which suggest that patients with BPD who are failing HFOV or conventional ventilation may experience dramatic improvement when treated with HFJV (Friedlich et al. 2003; Plavka et al. 2006). Patients with BPD and dilated, floppy airways are prone to airway collapse and air trapping when active exhalation is applied with relatively low mean airway pressure. The rationale for this apparent advantage of HFJV is the ability to ventilate with a very short I:E ratio, maintain airway patency with adequate PEEP, and avoid active exhalation. Additionally, because of the unique gas flow characteristics of HFJV, distribution of ventilation is relatively independent of regional differences in lung compliance.

19.1.2.8 Intraoperative Use of HFJV

HFJV has long been used for laryngeal surgery and ENT procedures, because it can be delivered through small catheter and minimize interference with the surgical field. These applications are mostly in adult patients (Lanzenberger-Schragl et al. 2000), but pediatric applications have been reported (Mausser et al. 2007). A second application is during intrathoracic surgery where lung motion interferes with the operative field. In the early 1980s we routinely utilized HFJV during

ligation of the patent ductus arteriosus at Children's Hospital of Akron, Ohio, because of the ease with which the left lung could be retracted and gas exchange could be maintained (Keszler, 2010). More recently Greenspan reported similar findings in a series of nine infants undergoing congenital heart disease palliation (Greenspan et al. 1994).

19.1.2.9 Interhospital Transport

The lack of a system of regionalized care in many parts of the United States results in substantial numbers of infants with severe respiratory failure being treated in community hospitals. When these infants eventually fail to respond to maximal therapy, they often require transport to a regional referral center for rescue therapies, such as iNO or ECMO: an infant who is failing on maximal support on HFV, transport on conventional ventilation is unfeasible or at best hazardous. For this reason, some NICUs that offer such rescue therapies have developed the capability to provide high-frequency ventilation during transport. Only two options are available: the Bronchotron flow interrupter (see Sect. 8.2.1.3.2.2) and the Bunnell HFJV. The jet ventilator is bulkier and requires battery power but is a device with an extensive track record of safety, has the ability to readily reproduce the settings that were in use at the referring hospital, and is familiar to the transport personnel from their use of it in the NICU. There is extensive anecdotal experience with HFJV on transport, including 15 years of use at Georgetown University hospital (Keszler, 2010), but only one publication describing its safety and effectiveness (Mainali et al. 2007).

19.1.2.10 HFJV in Older Infants and Children

Although the Bunnell Life Pulse is only approved for use in newborn infants, there are published reports of remarkably successful use in the pediatric population (Vernon et al. 1996; Kocis et al. 1992; Smith et al. 1993; Sarnaik et al. 1996). Because these are only small, uncontrolled series, no specific recommendations can be formulated, but it is of note that despite the artificial FDA-

imposed PIP limit of 50 cm H₂O, very sick children as old as 3.3 years were successfully supported with this device.

Conclusion

High-frequency jet ventilation is now generally recognized as an effective rescue therapy in a variety of causes of respiratory failure. Because of the extremely short inspiratory time and nature of gas flow in the larger airways, HFJV offers unique benefits over conventional and oscillatory ventilation in the treatment of air leak. Its portability makes it useful during interhospital transport. The role of HFJV as a primary mode of ventilation for prevention of chronic lung disease remains a subject of ongoing debate. Enthusiasm for HFJV as a primary mode of ventilation continues to be tempered by lingering concerns about the possibility of neurologic injury. At the same time, recent advances in conventional mechanical ventilation have led to some degree of convergence of HFV and tidal ventilation. This logical result of our improved understanding of respiratory pathophysiology has made the benefits of HFJV more difficult to discern in recent years.

Essentials to Remember

- There are good experimental and clinical studies to support a number of different indications for the use of HFJV.
- HFJV is an effective rescue treatment in infants with severe air leak and in infants with respiratory failure refractory to conventional ventilation.
- HFJV reduces lung injury when used in infants with uncomplicated RDS.
- Majority of the clinical studies were done in an era of much lower use of antenatal steroids and at a time when conventional ventilation was less sophisticated than it is today; therefore, the applicability of these studies to today's population is limited.

19.2 Tracheal Gas Insufflation (TGI)

Claude Danan and Xavier Durrmeyer

Educational Goals

- Continuous tracheal gas insufflation (CTGI) is an adjunct to conventional ventilation to treat the instrumental dead space problem (see Sect. 5.2.3). CTGI appended to pressure-controlled mechanical ventilation is a specifically designed technique aimed at decreasing ventilation parameters as pressures and tidal volume (Vt).
- To understand potential indications for CTGI, with a special focus on its use in premature infants.
- Immediate efficiency, feasibility, and long time use of CTGI in the clinical setting will be discussed.

19.2.1 Introduction

Continuous tracheal gas insufflation is an adjunct to conventional ventilation to treat the instrumental dead space problem. It is easy to understand that the situations without high “anatomic dead space/ tidal volume” ratio are not good candidates for CTGI. Intuitively, good candidates are the smallest neonates in whom instrumental dead space volume is very close to tidal volume, in the acute phase of the disease when compliance is very low. In older infants, instrumental dead space is usually not a problem, but some individual cases of acute lung diseases with very restrictive syndrome may necessitate helping CO₂ clearance without increasing ventilation aggressiveness. In general, large cohorts of preterm infants are natural candidates for CTGI. As it was shown in lung testing, CTGI is suspected to be really efficient in preterm infants, but at this time, there are no ventilators implemented with CTGI and no commercially available device useful for routine treatment with CTGI. Results and conclusions presented here are suggested from clinical trials conducted with non-patented devices. These devices are important to insure safety conditions to

avoid air leaks and to provide proper heating and humidification of alveolar gases. Safety conditions were described (Dassieu et al. 1998, 2000) and repeated in FDA recommendations. It is known that from part to part, some babies or older infants were rescued with TGI, outside of these recommendations, but these experiences were not published and are lost for knowledge.

19.2.2 Neonatal Indications

All references presenting TGI in neonates are from studies and trials conducted in Creteil, France (Dassieu et al. 1998, 2000; Danan et al. 1996, 2008). For all of them, TGI flow is continuous (CTGI), CTGI flow is conducted in an additional circuit molded in the wall of a specific endotracheal tube (ETT), a pump provides 0.5 L/min as it was designed during lung testing experiences, and a safety system avoids the risk for lung overinflation. The diagram assembly is drawn in Sect. 5.2.3.

Several pilot studies aimed at documenting efficacy and long-term effect of CTGI in order to define indications for CTGI in neonates and are presented below:

19.2.2.1 Efficacy of CTGI in Neonates

The inclusion criteria for the first ten babies treated with CTGI were postnatal age ≤ 5 days, weight $< 1,500$ g, and mean airway pressure ≥ 10 cm H₂O, as a surrogate for serious respiratory distress (Danan et al. 1996). For the whole group of ten, instrumental dead space was 4 mL, main tidal volume was 4.6 ± 2.1 mL, and for the entire group, the mean PaCO₂, after 30 min of TGI, was significantly lower than the mean pre-TGI PaCO₂ ($p \leq 0.0001$). The mean reduction was 12.1 ± 5.9 mmHg, i.e., 26 ± 12 % of the initial mean PaCO₂. The time course of TcPCO₂ showed that this decrease was reversible on discontinuation of TGI. Out of ten infants treated in the study, nine responded to TGI and presented with alveolar disease (HMD). One baby, despite a high mean pressure, did not present with alveolar disease and had a high pre-TGI VT. This subject's main problem was an excessively high

alveolar dead space. The inefficacy of TGI was therefore no surprise. On the basis of the $(\text{PaO}_2/\text{FiO}_2 \times 100)$ ratio, TGI did not induce any change in oxygenation ($1.8 \text{ mmHg} \pm 0.9$ vs. 1.9 ± 1 ; $p=\text{NS}$). High instrumental dead space/tidal volume ratio is the indication for CTGI. For these ten babies this ratio was 0.87.

19.2.2.2 Factors Influencing CTGI Efficacy in Neonates

CTGI efficacy is related with high anatomic dead space/tidal volume ratio, and its efficacy is increased in a context of hypercapnia and aggressive ventilation. In other words, CTGI is more efficient in smaller babies presenting with the most severe respiratory disease and requiring the most aggressive ventilation. If we consider permissive hypercapnia as a mode of lung protection, CTGI is synergistic with permissive hypercapnia. Finally the effect of CTGI on gas CO_2 elimination (i.e., efficacy) is immediate (Dassieu et al. 1998) as illustrated in Fig. 19.2.

During the PCO_2 reduction test (Fig. 19.2a), the PaCO_2 decrease correlated with VD/VT ratio

($r=0.54$, $p<0.005$) and baseline PaCO_2 ($r=0.58$; $p<0.002$). The decrease was not significantly correlated with the following parameters: weight, term, FiO_2 , and oxygenation index. During the PIP reduction test (Fig. 19.2b) keeping PCO_2 constant, the ΔP reduction was correlated with the baseline TcPCO_2 ($r=0.6$; $p<0.05$) and with baseline PIP ($r=0.57$; $p<0.05$).

19.2.2.3 Effect of CTGI During a Prolonged Period

As CTGI offers lung protection, it is logical to start CTGI as soon as possible. In piglets, only 4 h were sufficient to histological changes in the lungs of animals treated with CTGI (Randolph 2009; Kuo et al. 1996). In premature infants of less than 30 weeks of gestational age and randomly assigned to be treated by CTGI within 6 h of birth during their first 4 days of life (Dassieu et al. 2000), the peak pressure to PEEP gradient was reduced by 18–35 % in the CTGI group at each time point (Fig. 19.3a) with similar tcPCO_2 level (Fig. 19.3b) and with no difference in $\text{tcPO}_2/\text{FiO}_2$ ratio (mean $\pm$ SD 245 ± 29 vs. $261 \pm 46 \text{ mmHg}$)

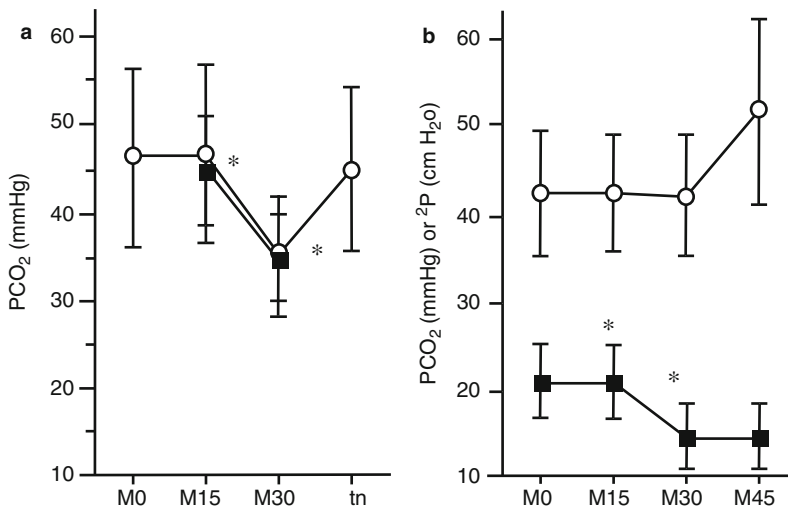


Fig. 19.2 PCO_2 reduction test (a) and PIP reduction test after 30 min of 0.5 L/min CTGI flow rate. For both figures the x-axes indicate the time in minutes: M0 (time zero) to M15 (15 min) indicates an observation period on IPPV. At M15, CTGI-0.5 was added for 15 min, and it was discontinued at M30 (30 min) followed by again 15 min IPPV only. All other ventilator settings were kept constants. (a) PCO_2 reduction test ($n=30$) (open circle TcPCO_2 , full

square PaCO_2 , * $p<0.0001$). (b) Pressure reduction test ($n=14$). During the CTGI period (M15 to M30), PIP was reduced in order to keep TcPCO_2 constant; the PIP diminution was performed in the first 5 min of this period. At M30 the CTGI was removed and PIP was not modified during the following 15 min (open circle TcPCO_2 , full square ΔP (PIP-PEEP); * $p<0.0001$)

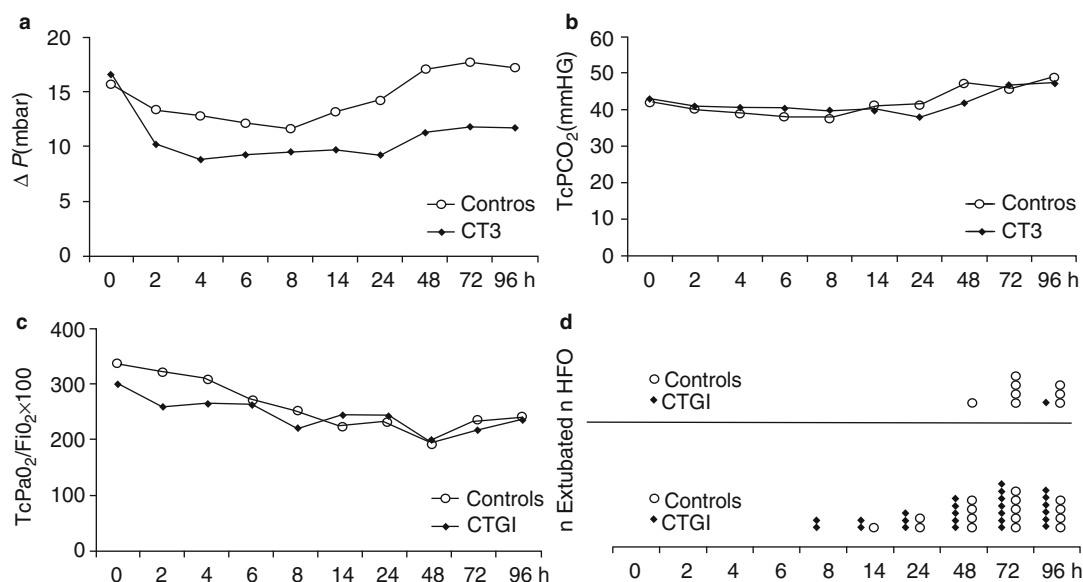


Fig. 19.3 Effect of CTGI on ventilatory and gas exchange parameters during the first 4 days of treatment. CTGI initiated within 6 h of birth and continued during the first 4 days of life: the peak pressure to PEEP gradient (ΔP) could be reduced at each time point (by 18–35 %) in the CTGI group (a) with similar transcutaneous PCO_2

($TcPCO_2$) levels (b) and with no difference in $TcPO_2/FiO_2$ ratio (mean $\pm$ SD 245 ± 29 vs. 261 ± 46 mmHg) (c). With the same extubation criteria, extubation was possible sooner in the CTGI group ($p < 0.05$) (d). The CTGI group required less often transition to rescue high-frequency oscillatory ventilation (HFO)

(Fig. 19.3c) over the first 4 days. With the same weaning and extubation criteria, extubation was possible sooner in the CTGI group when compared to controls ($p < 0.05$) (Fig. 19.3d). In this first long-term study using CTGI, CTGI allowed to use a low volume ventilation strategy over a long time period and to reduce the duration of mechanical ventilation (Dassieu et al. 2000).

In another population of preterm babies less than 28 weeks of gestational age, all of them immediately treated with CTGI and the same extubation criteria, a 36-h delayed extubation had no adverse effect and was associated to earlier definitive room air spontaneous ventilation without any support and shorter hospitalization length. Rather than to rush on extubation, providing a longer initial optimized mechanical ventilation including CTGI may protect the lung and prevent long invasive or noninvasive ventilatory support (Danan et al. 2008).

In summary, CTGI as adjunct to a lung protective ventilatory strategy may reduce lung ventilatory-induced lung injury and consequently allow to decrease the duration of ventilatory support

and in-hospital stay. This effect is especially marked in the smallest babies (Fig. 19.4).

19.2.3 Pediatric Indications

Whereas severe respiratory distress in low and extremely low-birth-weight infants might be a logical indication for CTGI, this is not as well documented for term newborns, toddlers, or children. In fact only a few pediatric patients were treated with CTGI during the 90th. Actually the recent management recommendations for severe pediatric ARDS include limitation of tidal volumes < 10 mL/kg, maintenance of pH between 7.30 and 7.45, and limitation of plateau pressure below 30 cm H_2O (Randolph 2009). In adults CTGI in conjunction with conventional mechanical ventilation has shown to be efficient in reducing hypercapnia (Kuo et al. 1996). Because of the lack of commercially available system and various technical problems difficult to deal with, CTGI was abandoned for this patient population and not developed for pediatric patients. However,

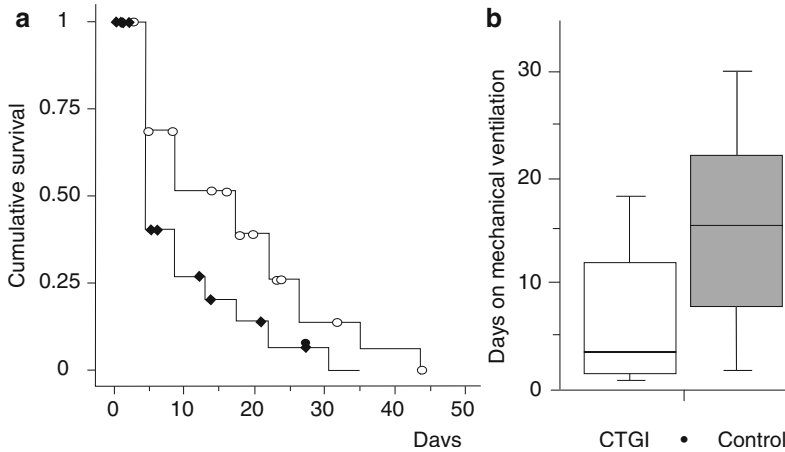


Fig. 19.4 Effect of CTGI on time of first extubation and total duration of mechanical ventilation: Survival curve applied to the first time of extubation with CTGI group symbolized by *full lozenges* and control group by *open circles*. The Log-Rank test, $p < 0.05$, indicated a significant difference between the two groups (a). Comparison

of the duration on mechanical ventilation for CTGI group on the left side and control group on the right side with the 10th, 25th, 50th, 75th, and 90th percentiles indicated for each group. The total number of days on ventilation (median, 25–75 quartiles) was 3.6, 1.5–12.0 days vs. 15.6, 7.9–22.2 ($p = 0.012$, Mann–Whitney test) (b)

one indication of CTGI still exists during venovenous extracorporeal membrane oxygenation (vvECMO). During vvECMO for extracorporeal CO_2 removal, oxygenation can be improved by apneic oxygenation with a continuous oxygen flow by CTGI. In this indication the CTGI flow is kept lower ($1 \text{ L/m}^2/\text{min}$) than dead space washout and is only used for optimizing oxygenation by passive diffusion (Chevalier et al. 1993).

Future Perspectives

Ventilators with CTGI option including appropriate security device and monitoring may be available soon. With such devices it should become easy to switch on CTGI and get immediate results on ventilation parameters, allowing to reduce peak airway pressures and tidal volumes. However, security features and monitoring must be implemented directly in the ventilator, and the oxygen fraction (FiO_2) in the additional gas used for CTGI has to be identical to the FiO_2 of the main circuit. However, adequate humidification remains a key issue

for its safe use, but this difficulty should be improved by new synthetic polymer systems that should allow this still existing problem. These latter systems are currently under investigation.

Essentials to Remember

- Continuous tracheal gas insufflation as an adjunct to mechanical ventilation was proved efficient in reducing PaCO_2 in neonates as in adults with respiratory distress.
- As a correlate, CTGI+conventional ventilation allows for V_t or pressure reduction to achieve a similar PaCO_2 as compared to conventional ventilation without CTGI.
- No patented device is available to date to permit its generalized use.
- Issues regarding system safety and proper gas humidification should be solved before spreading the technique.

19.3 Indications for Liquid Ventilation

Thomas H. Shaffer, Kevin Dysart,
and Marla R. Wolfson

Educational Aims

- Characterize the population of infants that are most suited for liquid ventilation techniques.
- Outline the physiological sequelae that have been associated with liquid ventilation procedures.

19.3.1 Introduction

Clinical trials investigating the use of perfluorochemical liquid ventilation in both critically ill adults as well as newborns have been conducted over the last 20 years. These trials have focused on patients with high morbidity and mortality rates related directly to their underlying lung dysfunction. In newborns many of the early trials from the late 1980s through the 1990s focused on patient populations in whom survival was doubtful (Greenspan et al. 1989, 1990; Leach et al. 1995; Gross et al. 1995; Hirschl et al. 1998). These early rescue trials relied upon clinical criteria to identify patients in whom traditional therapies were unlikely to yield success. This section will focus on the indications for use in several subgroups commonly encountered in newborn critical care. It is in these patients that PFC liquid ventilation has yielded the most promise as a therapy.

19.3.2 Very Low-Birth-Weight Infants (VLBW)

1. Liquid ventilation clinical ventilation trials have been most plentiful in this subpopulations of newborns. These trials have focused

upon critically ill newborns in extremis in whom survival is doubtful.

2. The indications for inclusion into these trials have historically been defined by extreme levels of illness severity. Inclusion criteria have included common clinical variables such as partial pressure of oxygen, partial pressure of carbon dioxide, calculated oxygenation index, and ventilator settings such as peak inspiratory pressure (PIP).
3. These common clinical variables will be used as we move forward using the perfluorochemical liquid ventilation. However, it is unlikely that we will continue to use such profoundly abnormal values.
4. For example, in a study conducted in 13 infants by Leach et al., infants were required to have a sustained need for an inspired fraction of oxygen of 1.0 and required mean airway pressures of 10, 12, and 14 for birth-weight categories of 600–1,000, 1,001–1,500, and 1,501–2,000 g, respectively (Leach et al. 1995).
5. It is likely that a modification of these parameters identifying at-risk patients with lower expected mortality rates will be used to identify extremely low-birth-weight infants who could most benefit from this therapy.

19.3.3 Extracorporeal Life Support

1. A small number of infants receiving extracorporeal life support (ECLS) have been treated with PFC liquid ventilation. Indications for treatment with liquid ventilation in this group of infants reflect the overall nature of clinical liquid ventilation trials to date in that infants were thought to be unlikely to survive.
2. Infants were already on ECLS and doing poorly for the most part at the time of liquid ventilation initiation.
3. The majority of infants were being treated for congenital diaphragmatic hernia (CDH) or acute respiratory distress syndrome as a result of either sepsis or meconium

aspiration syndrome (Gross et al. 1995; Hirschl et al. 2003).

4. The infants with CDH represent a unique group and a potential indication moving forward. The nature of the disrupted embryology and pulmonary hypoplasia along with the pulmonary vascular maldevelopment makes a liquid breathing medium as ideal option to improve both ventilation and oxygenation while maximally recruiting available alveoli and minimizing ventilator-induced lung injury.
5. Despite the limited experience with liquid ventilation in the population of infants on ECLS, the therapy has demonstrated enough promise in early human trials and the significant amount of animal research to offer another potential therapy to those infants failing ECLS (Hirschl et al. 2003).
6. A potential indication would be failure of ECLS to affect meaning and sustained changes in gas exchange after a sufficient period of time. Typically ECLS is utilized as a temporary therapy to allow healing of the lung parenchyma along with gradual reductions in pulmonary vascular tone such that infants can again be supported with conventional means.
7. In those infants, however, in whom ECLS is not achieving the stated goals, PFC liquid ventilation may find an indication is improving overall recruitment and stabilizing both ventilation and oxygenation.

19.3.4 Bronchopulmonary Dysplasia

1. No prior clinical trial has investigated the use of PFC liquid ventilation in children with bronchopulmonary dysplasia, but a potential indication in this population may exist.
2. Infants with BPD suffer a disease of disordered alveolarization, airway injury, and a

heterogeneous mix of overdistended and gas-trapped segments of lung in combination with atelectatic areas not participating in gas exchange.

3. PFC liquid ventilation may find an indication in these patients as the ability of the liquid to improve oxygenation and ventilation, while recruiting lung segments and improving ventilation-perfusion matching could be vital in improving the infants' overall health.

19.3.5 Summary

1. While no indications currently exist for PFC liquid ventilation, previous clinical and animal works provide clear guidance as to what the therapy can achieve and in which patients the therapy may be most useful.
2. Moving forward it is unlikely that the same illness severity seen in initial clinical trials will form the indication for treatment.
3. Once the therapy is defined as safe and effective in a variety of newborn populations and less critically ill neonates, hopefully it will find indications as not just lifesaving but disease-course altering.

Essentials to Remember

- Inclusion criteria for liquid ventilation include low arterial partial pressure of oxygen, high arterial partial pressure of carbon dioxide, and high peak inspiratory pressure (PIP).
- To date, liquid techniques have been shown to improve oxygenation and ventilation while recruiting lung segments and improving ventilation-perfusion matching which can be vital in improving the infants' overall health.

19.4 Negative-Pressure Ventilation: Clinical Applications

Francesco Grasso and Brian P. Kavanagh

Educational Aims

- Negative-pressure ventilation is a noninvasive ventilator technique which is able to reliably guarantee gas exchange without the need for endotracheal intubation.
- When pulmonary blood flow is passive or impaired, restoring spontaneous ventilation and early extubation can improve the perfusion because of enhanced preload.
- Negative-pressure ventilation when applied to the chest only may mimic spontaneous ventilation and can be helpful in early postoperative state.
- Despite being used successfully for treatment of neonatal RDS or bronchiolitis, no studies to date have demonstrated superiority over conventional ventilation.
- Negative-pressure ventilation may be a valid alternative to noninvasive positive-pressure ventilation in long-term care, as it is better tolerated and enables speech and eating.

19.4.1 Introduction

Negative-pressure ventilation (NPV) works by exposing the chest wall to subatmospheric pressure which is able to lower the pleural pressure and generate a tidal volume. NPV can be applied as continuous negative end-expiratory pressure (CNEP) or as NPV plus CNEP, where the negative pressure is generated during the inspiration and maintains constant during the expiration. Over the past 50 years, NPV has found numerous

applications in clinical practice especially in the treatment of the postoperative cardiac patients because of hemodynamic effects. At the same time NPV can be used in the treatment of bronchiolitis, RDS, ARF, and for long-term ventilation. In these clinical scenarios NPV appears to be effective as positive-pressure ventilation in terms of gas exchange but with the advantage of not requiring endotracheal intubation, thereby potentially lessening the risks of ventilator-associated pneumonia.

19.4.2 Negative-Pressure Ventilation (NPV) and Cardiac Patients

Positive-pressure ventilation is the commonest approach to perioperative respiratory support for pediatric cardiac patients. It is well known that positive pressure decreases ventricular afterload, which can be helpful where low cardiac output is caused by LV dysfunction or AV valve regurgitation. Unfortunately, this is accompanied by inhibition of venous return and pulmonary blood flow induced by the increased intrathoracic pressures. Recently, several authors investigated the role of negative-pressure ventilation on the cardiovascular system both in patients with normal heart function and in those with low cardiac output (Shekerdemian et al. 1997b, 1999, 2000). In general, NPV is as effective as PPV in oxygenation and clearing CO₂ but has the additional potential advantage that augmented preload and may improve overall cardiac output (Roos et al. 1961).

The effects of CNEP (continuous negative end-expiratory pressure) on cardiac output in small infants with normal hearts were investigated, where the negative pressure was applied using a tank ventilator (Raine et al. 1993). No difference in terms of cardiac output was found, and the lack of effect may be attributable to the device used (Lockhat et al. 1992), as whole-body tank ventilators do not increase preload because of the

equal effects (in contrast to chest-only devices) on the inferior vena cava (i.e., below the diaphragm) and on the superior vena cava (i.e., above the diaphragm). A comparison made between positive-pressure and negative-pressure ventilation in children with normal hearts vs. those who had undergone cardiac bypass without any residual shunts was investigated (Shekerdemian et al. 1997a). PPV and NPV were matched in order to provide the same minute ventilation and CO₂ removal, but the NPV was applied using a chest-only device. Because of increased right ventricular preload, which led to increased pulmonary blood flow (and left ventricular preload), the cardiac output and MvO₂ were increased in both groups. In addition to increased preload, there may be an additional selective effect on PVR because infusion of colloid to increase the RV volume to the same dimensions during positive ventilation did not restore fully the cardiac output (Henning 1986). The difference between PPV and NPV can likely be attributed to increased ventricular preload and possibly to a reduction in PVR.

Cardiorespiratory interactions are crucial when the pulmonary blood flow is passive, as in patients with a cavo-pulmonary shunt. In bypassing the heart, pulmonary perfusion becomes passive and thus more dependent both the upstream (i.e., caval) flow and the downstream (i.e., pulmonary) vascular resistance. Indeed, the increased flow in the Glenn circulation that is associated with mild hypercapnia suggests that cerebral vasodilatation (resulting in increased flow into the superior vena cava, the Glenn inflow) overcomes any effects that hypercapnia may have in increasing PVR (the Glenn outflow) (Hoskote et al. 2004). This illustrates the relative importance of inflow (usually more important) vs. outflow (usually less important) control in perfusion in patients with cavo-pulmonary connections.

In patients with Fontan physiology, the forward flow in the pulmonary artery is increased with spontaneous inspiration (i.e., negative – reduced intrathoracic pressure), and in contrast, it is decreased during the expiratory phase (i.e.,

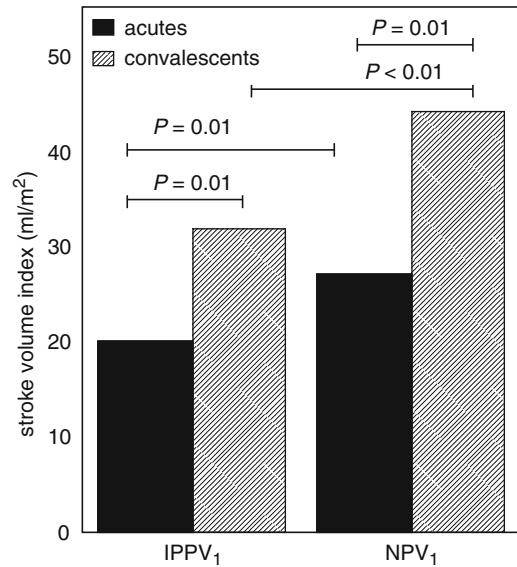


Fig. 19.5 Stroke volume index during standard studies. The stroke volume was significantly lower for acute patients during IPPV (IPPV₁) and NPV (NPV₁). There was a significant improvement in stroke volume during NPV in both groups of Fontan patients. This is explained by increase right heart preload. The increased pulmonary blood flow is responsible for the increased stroke volume (From Shekerdemian et al. 1997b)

positive – increased intrathoracic pressure) (Penny and Redington 1991). In postoperative Fontan patients, a low cardiac output state remains a primary cause of morbidity and mortality. NPV may effectively ventilate the lungs while maintaining constant negative intrathoracic pressure. This leads to an increased pulmonary blood flow which in turn leads to an increased stroke volume and better overall perfusion with higher levels of global oxygen delivery (Fig. 19.5) (Shekerdemian et al. 1997b).

Restrictive right ventricular physiology can complicate surgical repair of tetralogy of Fallot, where the stiff right ventricle causes diastolic dysfunction. Doppler studies have demonstrated antegrade diastolic pulmonary blood flow (in effect, flowing *through* instead of *filling* the right ventricle) corresponds to reduced right ventricular diastolic compliance and a low cardiac output. Such patients can require prolonged intensive care with ongoing fluid loading (Cullen et al.

1995). In these situations, NPV may be particularly beneficial by increasing the cardiac output through improved right ventricle filling. Indeed, the most sustained improvements with NPV have been reported in patients with restrictive (vs. nonrestrictive) right ventricular physiology (Shekerdemian et al. 1999, 2000).

Finally, combined modes of ventilation (i.e., conventional positive pressure with continuous negative pressure instead of PEEP) can provide adequate oxygenation and cardiac output in patients following cardiac surgery with normal left ventricular function (Chaturvedi et al. 2008).

19.4.3 Noninvasive Ventilation in Respiratory Failure: Positive vs. Negative

Noninvasive ventilation has been studied in adults with benefits in terms of gas exchange, decreased rate of intubation, and possibly less nosocomial infections. Unfortunately, in the pediatric population the literature is more limited. Among noninvasive options, the basis for choosing negative- (NPV) vs. positive-pressure ventilation (PPV) includes better hemodynamic stability and the possibility of preserving important physiological functions such as speech, swallowing, and feeding. In addition, because the airway is not instrumented, suctioning or fiberoptic bronchoscopy may be easier during NPV rather than during positive-pressure mask ventilation. Review of NPV in children with hypoxemic respiratory failure is hampered by a paucity of data (Shah et al. 2013).

19.4.4 Negative End-Expiratory Pressure (NEEP) and Bronchiolitis

Bronchiolitis is characterized by patchy involvement of the airways, including the smaller bronchioles. Critical elements include airway obstruction due to edema, infiltration, and secretions which leads to air trapping or/and complete

obstruction with subsequent atelectasis. Younger children (especially <2 years) are particularly affected because of the smaller size of the airways coupled with the greater chest and lung compliance (Panitch 2001). Mechanical ventilation is often needed because of hypoxemia and fatigue or, especially in very young infants, because of the propensity to apneic episodes.

Theoretically NPV could prevent airway collapse because the negative extramural pressure serves to keep the airways distended and therefore patent. However, this has neither been tested nor proved. Currently, noninvasive positive-pressure ventilation is the first choice for assisted ventilation in children with bronchiolitis (Sekar and Corff 2009); the conventional positive-pressure devices demonstrate good performance in older children but still fail to universally guarantee an effective increase in transpulmonary pressure especially when not provided with a ventilator (Kahn et al. 2007), whereas NPV may provide it more reliably (Alexander et al. 1979).

Clinical studies show that in the acute phase of bronchiolitis, early use of NPV is associated with decreased O₂ requirements and a lower rate of endotracheal intubation, compared with use of supplemental O₂ alone (Hartmann et al. 1994b). Indeed a reported low rate of intubation (0.4 %) when NPV is rapidly initiated (Samuels 1998) is corroborated by retrospective data (Al-balkhi et al. 2005) (Henderson 2005).

19.4.5 Negative-Pressure Ventilation (NPV) in Neonatal Respiratory Distress Syndrome (RDS)

Respiratory distress syndrome is characterized by an effective lack of surfactant resulting in increased surface tension at the air-liquid interface, thereby making the alveoli prone to collapse (Sekar and Corff 2009). Administration of exogenous surfactant – in addition to recruitment – is the key management intervention. At the present time the standard initial line of treatment is continuous positive airway pressure (CPAP) to augment lung recruitment (Sekar and Corff 2009),

often enabling avoidance of endotracheal intubation and its associated complications. Indeed there appears to be little difference in outcome (i.e., mortality, development of bronchopulmonary dysplasia) in preterm infants treated with CPAP vs. endotracheal intubation (Morley et al. 2008).

Negative-pressure ventilation may be an alternative to the conventional noninvasive positive-pressure approach. This has been investigated in several studies. Two studies from the 1970s showed that negative ventilation compared with O₂ therapy alone was effective in improving oxygenation and reducing the rate of intubation (Faranoff et al. 1973) (Outerbridge et al. 1972). In 1979 the first comparison of CPAP (delivered using a nasal mask) vs. negative end-expiratory pressure (NEEP, delivered using a tank ventilator) reported no differences in oxygenation, hemodynamics, or in the duration of ventilation; however, negative pressure was associated with a more rapid increase in oxygenation (Alexander et al. 1979). More recently, larger studies indicate that continuous negative expiratory pressure (CNEP) is a valid alternative to positive-pressure ventilation, even when used as a second line of treatment after failure of conventional ventilation (Cvetnic et al. 1990). Why the application of continuous negative end-expiratory pressure may be more effective than PEEP is still unclear, although use of a tank ventilator (applying negative pressure equally above and below the diaphragm) to provide NEEP should minimize any hemodynamic advantage. However, NEEP might provide more effective lung recruitment than PEEP, and if that is the case, it may thereby more effectively reduce shunt and lessen venous admixture.

A large randomized controlled trial (Samuels et al. 1996) reported that CNEP improved clinical outcome (i.e., a composite clinical score incorporating mortality, oxygen requirements, and complications). A secondary outcome was the suggestion that NPV could reduce the duration of need for supplemental, which might translate into a lower incidence of chronic lung disease. However, concerning increases were reported in mortality, barotrauma, and abnormalities on cranial ultrasound. Finally, a long-term (10 years) follow-up study compared neurological, cognitive, and disability

outcome in the same patients (Samuels et al. 1996) and reported no long-term differences compared with infants who had received standard treatment (Telford et al. 2006).

19.4.6 Negative-Pressure Ventilation in Acute Respiratory Failure (ARF)

The effect of negative-pressure ventilation is well established in newborns with severe respiratory distress syndrome; however, less information is available about NPV in the treatment of acute respiratory failure in older children (or in adults). Most data have come from studies in immune-compromised patients with ARF (Sanyal et al. 1975, 1977a; Harris et al. 1978). Negative-pressure ventilation applied as CNEP has been studied in spontaneously breathing children, with the level of negative pressure based on patient comfort and gas exchange. In this setting, CNEP appears to be beneficial in terms of oxygenation and work of breathing.

No pediatric studies to date have compared CNEP with CPAP (applied via a face mask). Mortality has been compared retrospectively in patients undergoing CNEP vs. those receiving standard medical treatment, and the data suggest a mortality benefit (mortality 11 % vs. 31 % in the standard treatment) associated with CNEP (Sanyal et al. 1977b).

In a case report where CNEP was initiated after CPAP in an adult patient with ARF who was intolerant to the face mask, no difference was found in terms of gas exchange (Morris and Elliott 1985). Only one paper has compared the effects of CNEP and CPAP in spontaneously breathing adult patients with acute lung injury (Borelli et al. 1998). In this case the amount of end-expiratory pressure applied as either positive or negative pressure was chosen in order to obtain comparable levels of trans-pulmonary pressure; no differences were found in terms of gas exchange or lung volume (Borelli et al. 1998).

CNEP may provide effective ventilation in pediatric patients with acute respiratory failure because it appears able to expand the lungs,

providing an adequate increase in functional residual capacity (FRC). Whether CNEP is as effective as CPAP remains to be investigated. Negative-pressure ventilation appears to be as effective as positive (invasive) ventilation in supporting patients with ARDS, and because intubation is not required, it may (in the absence of aspiration) reduce the propensity for development of ventilator-associated pneumonia.

19.4.7 Negative-Pressure Ventilation (NPV) and Long-Term Use

Continuous negative expiratory pressure (CNEP) has been used as long-term ventilatory assistance in children with obstructive sleep apnea, central hypoventilation syndrome, or neuromuscular disorders that result in hypoventilation. Overall, NPV appears to be as effective as positive ventilation in providing augmenting gas exchange and respiratory assistance without the disadvantages of a face mask or a tracheostomy (Jackson et al. 1993).

In central hypoventilation syndrome, NPV can successfully provide ventilator support and appears to improve quality of life by allowing the child to eat and communicate while receiving assisted ventilation (Hartmann et al. 1994a). A 5-year follow-up in patients with chest wall or neuromuscular diseases who were ventilated at home with negative-pressure ventilation indicated a stable status over the review period in terms of oxygenation, CO₂ control, and neurologic state (Jackson et al. 1993).

In conclusion negative-pressure ventilation appears to be a valid alternative to the commoner positive-pressure approach and may avoid the need for face mask ventilation or use of a tracheostomy. Although NPV could improve overall quality of life, there are no recent comparative data.

19.4.8 Unknown Issues

Despite a long history and extensive knowledge and experience with NPV, several aspects of negative ventilation are still poorly understood,

including the relationship with respiratory (chest wall) mechanics. NPV appears to be as efficient or more so as positive ventilation, whether applied as CNEP or when used as CNEP in conjunction with positive inflation. Recent studies suggested a possible role of NPV in reducing lung injury, but these laboratory studies require confirmation. More data are needed in order to understand the relationship between NPV and pulmonary edema. Finally, much evidence is retrospective and from small studies.

Essentials to Remember

Negative-pressure ventilation has, in several decades, been almost completely replaced by positive-pressure ventilation. Negative pressure is able to guarantee effective ventilation (in the absence of severe lung injury) with the potential advantages of not requiring intubation and perhaps less sedation. Negative-pressure ventilation has been successfully used in treatment of bronchiolitis and neonatal RDS, but little published data exist regarding ARDS. Because negative-pressure ventilation (when applied to selectively to the chest) can augment right ventricular filling and pulmonary perfusion, it may be helpful in the management of patients with low cardiac output state or postoperative patients following repair of tetralogy of Fallot or with cavo-pulmonary connections.

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Respiratory Support in Developing Countries Where Resources Are Limited

20

Trevor Duke

Educational Goals

- Review the definition of hypoxemia that might require oxygen therapy in various conditions.
- Review the basic rules on how and when to wean oxygen therapy.
- Review the concept of a stepwise approach towards respiratory support (noninvasive and invasive methods).
- Review the use of adjuvant nonventilatory treatment options for respiratory failure in children and neonates.

20.1 Oxygen Therapy

20.1.1 Definition of Hypoxaemia and Indications for Oxygen Therapy

The range of means for haemoglobin–oxygen pulsed saturation (SpO_2) at sea level is 97–99 %, with the lower limits (mean, 2 SD) being 94 % (Lozano 2001). Therefore, the normal range at sea level is 94–100 %. The normal range of SpO_2 becomes progressively lower in populations living in mountainous regions because of lower PaO_2 at higher altitude (see Fig. 20.1) (Lozano 2001). This was estimated using data from 16 studies in children outside the neonatal period. The continuous line predicts the level of SpO_2 below which oxygen should be given at different altitudes.

Changing the point at which hypoxaemia is defined and oxygen is given results in a major variation in the amount of oxygen used. A report from one hospital found that 13 % of children with pneumonia were hypoxaemic using a definition of $\text{SpO}_2 < 85$ %, 26 % were hypoxaemic using $\text{SpO}_2 < 90$ and 44 % were hypoxaemic using $\text{SpO}_2 < 93$ % (Laman et al. 2005).

The best cut-off point for giving supplemental oxygen may be the level of blood oxygen that is associated with increased morbidity or risk of death or delayed recovery, rather than a certain level of haemoglobin–oxygen saturation below normal for the population. With normal cardiac output, haemoglobin concentration and pH, arterial oxygen saturations of 68 % or more are prob-

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Fig. 20.1 Threshold of hypoxaemia at different altitudes

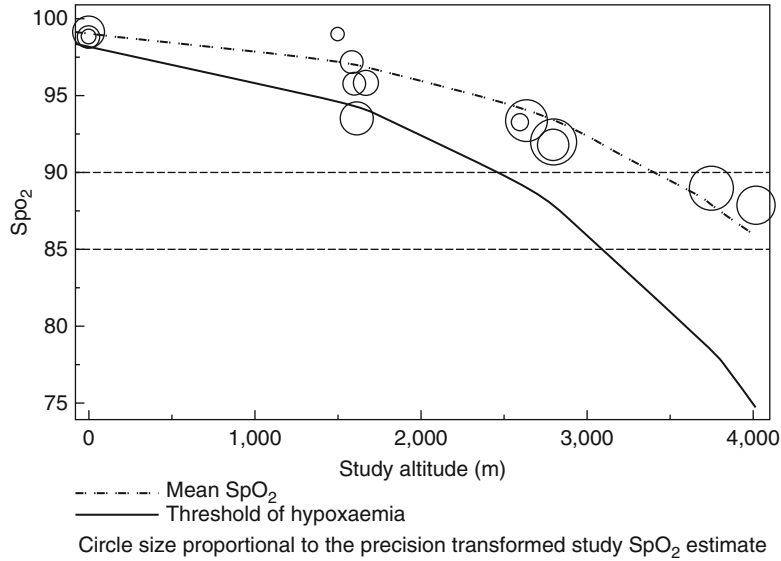
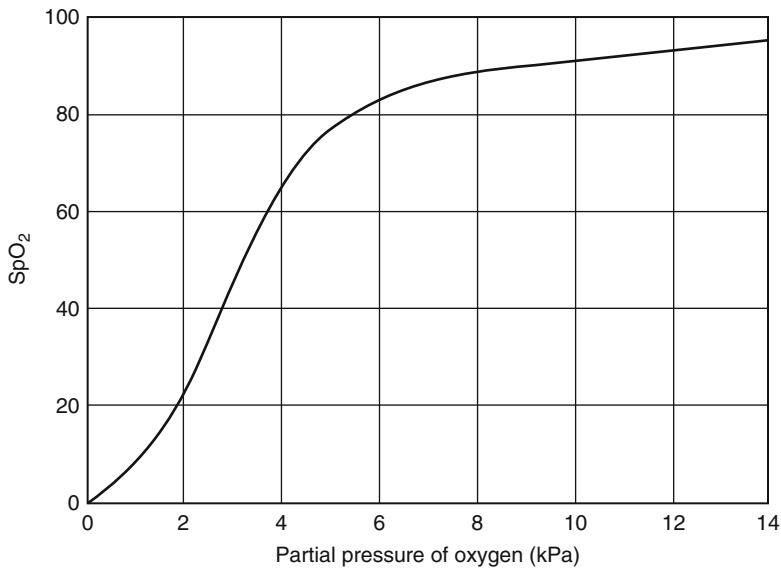


Fig. 20.2 Haemoglobin–oxygen dissociation curve



ably not dangerous (Nunn 1993). However, there are few data about the exact SpO₂ below which the risk of adverse outcomes increases. This risk will be different for different ages, disease states and comorbidities and at different altitudes, and a safe margin for error is required.

The gold-standard measure for the oxygen content of the blood is the arterial oxygen tension or PaO₂ (measured in mm Hg or kilopascals). PaO₂, however, can only be measured by blood

gas analysis. This method is invasive, painful and distressing to the patient, and blood gas machines and reagents are very expensive and, therefore, not appropriate in most district hospitals in developing countries. Therefore, we use SpO₂, which is related to PaO₂, to define hypoxaemia in these guidelines (see Fig. 20.2).

In practice, most studies have adopted a threshold at which to give oxygen of SpO₂ <90 %. This corresponds to the beginning of the steep part

Table 20.1 Clinical indications for oxygen therapy

Clinical presentation for severe pneumonia with	Priority for oxygen
Central cyanosis	Very high priority
Decreased consciousness, unresponsiveness or responsive to painful stimuli only	Very high priority
Head nodding or grunting	Very high priority
Severe palmar or conjunctival pallor (severe anaemia) with severe lower chest wall indrawing or fast breathing	Very high priority; high priority should also be given to urgent correction of the underlying abnormality (i.e. blood transfusion and/or antimalarials)
Acute coma or convulsions lasting more than 15 min	Very high priority until respiratory effort has returned to normal; also protect airway and ensure adequate ventilation
Inability to drink or feed	High priority
Severe chest indrawing	Priority

of the haemoglobin–oxygen dissociation curve, which is shown in Fig. 20.2. Small reductions in SpO₂ below 90 % may represent dangerous falls in PaO₂. This represents a safe margin for error where oxygen supplies are sufficient.

There will be conditions that require oxygen therapy at higher thresholds than 90 % SpO₂. These are conditions where oxygen delivery from the lungs to body tissues is seriously impaired or where vital organs may be particularly susceptible to low oxygen levels. Examples include severe anaemia, severe heart failure, severe sepsis or brain injury. In these conditions, many clinicians recommend giving oxygen if the SpO₂ is <94 %.

It is important to note that small changes in SpO₂ between 90 and 100 % reflect large changes in PaO₂, because the haemoglobin–oxygen dissociation curve is relatively flat. Below an SpO₂ of 90 %, however, the curve is steep and small falls in PaO₂ may result in much larger falls in SpO₂.

The clinical signs of hypoxaemia have been evaluated in many studies and reviewed (Rojas et al. 2009; Ayieko and English 2006). In situations where the oxygen supply is very limited, for children aged over 2 months, provide oxygen

according to the priority listing suggested in Table 20.1. Infants aged <2 months with signs of severe respiratory distress (tachypnoea, severe chest indrawing, head nodding or grunting) should be given oxygen because hypoxaemia puts them at greater risk of apnoea and death.

Even the best combinations of clinical signs commonly misdiagnose hypoxaemia in some patients with normal oxygen saturation or fail to detect some hypoxaemic patients. Pulse oximetry has been found to correctly identify 20–30 % more children who have hypoxaemia than will be found using clinical signs alone (Usen et al. 1999; Weber et al. 1997; Duke et al. 2002a). When used correctly, pulse oximetry provides reliable monitoring with little or no distress to the patient; in industrialized countries, it is the accepted standard for detecting hypoxaemia (Schnapp 1990).

When monitoring with oximetry, as a general rule, any child with an SpO₂ <90 % should receive oxygen. This rule best applies to health facilities located between sea level and 2,500 m above sea level and where oxygen supplies are ample (such as when using concentrators) for altitudes higher than 2,500 m.

Where there is sufficient oxygen to treat all children with hypoxaemia, it is the practice in some hospitals to give oxygen if the SpO₂ is <93 %. Some doctors suggest oxygen should be “discretionary” between an SpO₂ of 90 and 92 % and “mandatory” at SpO₂ <90 %. There are certainly some children who will benefit more than others from oxygen when the SpO₂ is in the range of 90–92 %: those with very severe anaemia, severe heart failure, septic shock and acute neurological illness. These children will be less able to withstand moderately low oxygen levels than children with only lung disease.

Because the normal SpO₂ range is lower at higher altitudes, it may be appropriate to only give oxygen for an SpO₂ of 85 % or less to children living at an altitude above 2,500 m, if oxygen supplies are limited (e.g. when using oxygen cylinders and transport difficulties or cost limit supply) (Duke 2003). Oxygen concentrators, which provide continuous, unlimited oxygen, largely overcome this problem. If these are available, a universal threshold of 90 % SpO₂ will be appropriate.

20.1.2 What to Do if the Child Does Not Improve or Deteriorates After Oxygen Is Given

It is very important that after starting oxygen therapy, the child is checked within 15–30 min to see if the treatment is working. In severely hypoxaemic children, correction may not be complete and clinical signs may remain, or the SpO₂ may still be low. This does not mean that oxygen therapy has failed and should be abandoned. Other children will deteriorate rapidly or slowly despite receiving oxygen. There are a number of possible causes for a lack of response.

Oxygen delivery is inadequate, so check that:

- Flow is occurring (hold the tubing close to your face to feel the flow).
- There are no leaks from oxygen tubing.
- The nasal prongs or nasal catheter are fitted correctly and not blocked.
- If delivery is via an oxygen concentrator, the concentration of oxygen being delivered is adequate (>85 %).

There are other problems (see the *WHO Pocket Book of Hospital Care for Children*, Chapter 4) (World Health Organization 2005), such as:

- Pleural effusion. Listen with a stethoscope for breath sounds on both sides of the chest; do a chest X-ray.
- Pneumothorax. Listen with a stethoscope for breath sounds on both sides of the chest; do a chest X-ray.
- Upper airway obstruction (e.g. from croup or a foreign body). Listen for stridor.
- Bronchospasm (e.g. severe asthma). Listen with a stethoscope for wheeze.
- Cyanotic heart disease or congestive heart failure.
- Ventilatory failure. The child's respiratory effort is inadequate; the child will have slow or shallow breathing and be lethargic.

If nasal prongs are being used at maximum flow and the child is still hypoxaemic, sometimes it is useful to give a second source of oxygen, if it is available, via an oxygen mask (ideally with reservoir bag) to increase the fractional concentration of inspired oxygen.

If a second source for mask oxygen is not available, an N-P catheter can give a higher fractional concentration of inspired oxygen than

nasal prongs (but never use nasal prongs and an N-P catheter together).

20.1.3 Monitoring the Progress of Children on Oxygen

In most hospitals, the most appropriate form of monitoring will be regular checks with pulse oximetry on children who might need oxygen, those who are already on oxygen, those who have developed respiratory distress and those who show other clinical signs of deterioration. Oximetry can also be used to determine how long children need to be treated with oxygen. In severe pneumonia the duration of hypoxaemia may be anything from several hours to several weeks; the usual time is 2–5 days (Duke et al. 2000, 2002b). The duration of hypoxaemia may be longer at higher altitudes than at sea level for a similar severity of pneumonia (Weber et al. 1995).

Children who are receiving oxygen should be monitored clinically at least twice a day with pulse oximetry. Children in a stable condition should be tried off oxygen once a day to determine if they still require oxygen.

It is important to be aware that pulse oximeters provide no information on carbon dioxide concentration in the blood and thus no direct information on ventilatory efficiency. It is unlikely that a child who has normal oxygen saturation while breathing room air has impaired ventilation. However, once oxygen is administered, SpO₂ can be maintained at normal levels despite severe hypercapnoea. In a child receiving supplemental oxygen, oximetry cannot be used to monitor the adequacy of ventilation. For children receiving oxygen, therefore, clinical monitoring of respiratory effort, respiratory rate and consciousness level is a better guide to the adequacy of ventilation. A child with inadequate ventilation will have slow or shallow breathing and be lethargic.

In a small hospital, any concern over the adequacy of ventilation should prompt efforts to ensure that the airway is clear and protected and that the patient is positioned to facilitate chest expansion (e.g. sitting in a semi-recumbent position of 20–30°, head up to reduce diaphragmatic splinting if there is abdominal distension, passing a nasogastric tube to deflate the stomach).

Referral to a high-dependency area or intensive care unit should be arranged if CPAP or mechanical support is available.

All methods of oxygen administration need supervision by trained personnel to detect and manage complications appropriately. A nurse should check every 3 h that the prongs or catheter are in the correct position and not blocked with mucus, that all connections are secure, that the oxygen flow rate is correct, that the airways are not obstructed by mucus and that there is no gastric distension. Prongs or catheters should be removed and cleaned at least twice a day.

All severely ill children need regular monitoring of vital signs and general condition. Many deaths in hospitals occur overnight, often when monitoring is infrequent or absent. SpO₂ is the most vital of clinical signs, so pulse oximetry is an invaluable, routine monitoring tool.

20.1.4 Trials Off Oxygen and When to Stop Oxygen

At least once each day, children in the ward who are clinically stable (have no emergency signs and SpO₂ >90 %) should be disconnected from oxygen for 10–15 min and carefully examined for changes in clinical signs and SpO₂, to assess whether supplemental oxygen is still required. Trials off supplemental oxygen are best done first thing in the morning, when there is likely to be adequate staff to observe the child throughout the day. If trials off supplemental oxygen are started in the late afternoon, low staff numbers overnight and the oxygen desaturation that sometimes occurs during sleep mean that there is a risk of hypoxaemia developing unrecognized overnight.

Children who have an SpO₂ <90 % while still on oxygen or who are unstable or very unwell should not be given trials on room air.

Before a trial off oxygen, the SpO₂ should be checked to determine if the trial is safe (i.e. SpO₂ >90 %). The child should then be disconnected from the oxygen source and observed carefully to avoid any adverse complications of hypoxaemia. If severe hypoxaemia (SpO₂ <80 %), apnoea or severe respiratory distress occurs, children should be immediately restarted on oxygen. Some children will become hypoxaemic very

rapidly when they are taken off oxygen, and this is a marker of very severe disease and a high risk of death. Parents and nursing staff should be advised to watch the child to see if he/she develops cyanosis or severe respiratory distress.

Where oxygen supplies are ample, children should receive supplemental oxygen until their SpO₂ on room air is 90 % or greater. If the SpO₂ is 90 % or more after a trial on room air, they should remain off oxygen and the SpO₂ should be rechecked after 1 h, as late desaturation can sometimes occur. Any child who appears to deteriorate clinically should have their SpO₂ checked to determine whether they need oxygen. If bed space allows, children should not be discharged until their SpO₂ has been stable at 90 % or more while breathing room air for at least 24 h, until all danger signs have resolved and until appropriate home treatment can be organized. This of course does not apply to children with cyanotic congenital heart disease, who have chronic hypoxaemia. For children with right to left intracardiac shunts (such as tetralogy of Fallot), oxygen will not be effective in relieving cyanosis or improving SpO₂.

The chest X-ray appearance does not provide any useful guide to the need for oxygen therapy or when it is appropriate to stop.

20.1.5 General Care for Children with Hypoxaemia or Severe Respiratory Distress

Nursing care of children with hypoxaemia is very important. The following describes the main things to consider, including minimal handling, positioning, fluids and nutrition and close monitoring.

20.1.5.1 Minimal Handling

Handling can be upsetting to severely ill children, and activity consumes more oxygen. Handling should be gentle, and unnecessary stress or painful procedures should be avoided.

20.1.5.2 Positioning

Children will often find their own most comfortable position in the bed or on their mother's lap, but sometimes their breathing may improve if they are nursed with their head raised about 30 ° with neck support, rather than lying flat. Some

hypoxic neonates and young infants may be more stable in the prone position, as long as their face is not obstructed.

20.1.5.3 Fluids and Nutrition

The following guidelines should be followed when dealing with fluids and nutrition of hypoxaemic children:

- Withhold oral feeds while the child has severe chest indrawing or severe respiratory distress because of the risk of aspiration.
- Use an intravenous drip or a nasogastric tube, depending on what can be managed most safely.
- Do not give large volumes of intravenous fluids as this may make the lungs “wet” and worsen hypoxaemia.
- Do not give large nasogastric feeds to children with severe respiratory distress, because the child may vomit and aspirate.
- Make sure that as soon as severe respiratory distress has settled, the child receives good nutrition, preferably breast milk.

20.1.6 Overcoming Parents' Concerns About Oxygen Use

Education of parents about the need for oxygen is important to alleviate fears. Many parents are afraid of oxygen and oxygen catheters. Sometimes they will have seen other children receive oxygen just before they died, and they may fear that the oxygen caused the death. It can be very helpful to show parents the pulse oximeter in operation and explain to them why the child's oxygen level is low. It is useful also to show them the clinical signs (such as chest indrawing or cyanosis of the gums or tongue). When oxygen is then applied, parents will see that the SpO₂ increases and the child's respiratory distress lessens. They will have much more confidence in the treatment and be more likely to accept it. In one hospital in Papua New Guinea, the absconding rate of mothers fell significantly (from about 25 % down to 8 %) when daily checking of children using pulse oximetry was introduced (Duke et al. 2000, 2002b). This was mostly the result of explanation of the monitoring and its implications (for needing oxygen, needing to stay in hospital or readiness for discharge). It is

also a daily demonstration that some special attention is being paid to their child, and mothers appreciate this greatly. Even when illiterate, most of these mothers were still able to understand the significance of the number generated by the pulse oximeter and thresholds for safe discharge when these were explained in their own language.

20.1.7 Sources of Oxygen

The most common sources of oxygen are oxygen cylinders, oxygen concentrators and oxygen pipelines.

Oxygen for cylinders is produced by cooling air until it liquefies, then distilling the liquid to separate pure oxygen from it. This is an expensive, energy-consuming process that can only take place in large manufacturing plants. Cylinders need to be transported to and from the bulk supply depot for refilling. Transport is difficult, expensive and often unreliable in developing countries, so small hospitals can be without oxygen supplies for long periods.

Oxygen concentrators entrain air from the environment, which usually contains 21 % oxygen, 78 % nitrogen and 1 % other gases. By extracting nitrogen from the air, they can produce almost pure oxygen. Most concentrators supply oxygen at a concentration of 90–96 %. In paediatric care, with a continuous and reliable power source, one oxygen concentrator can supply continuous oxygen for up to four patients. (In case of power failure, a power generator or a power-independent oxygen source should be available as a back-up.) Concentrators need regular maintenance to ensure proper function, but they are a reliable and independent oxygen source that is also cost-efficient. To get the most out of concentrators, they should be used with flow splitters or flow meters that allow oxygen to be provided to multiple patients at the same time.

In many larger hospitals, oxygen is distributed through a system of copper pipes from a central source of oxygen, usually located outside the building. The source may be liquid oxygen, high-pressure gaseous oxygen cylinders, a large oxygen concentrator or a combination of these. Pipeline systems supply oxygen at high pressure,

which enables equipment such as anaesthetic machines and ventilators to be supplied with the gas. A pipeline system has many safety advantages: it reduces the risk of fire and avoids handling and transportation between hospital wards of heavy cylinders. However, the high cost of installing centralized oxygen sources with copper pipelines and their maintenance make these systems of oxygen delivery unsuitable for district-level hospitals in developing countries.

20.1.8 Devices for Giving Oxygen

Methods for giving oxygen may be noninvasive (delivery through a face mask, into a head box, incubator or tent or through tubing held close to an infant's face) or semi-invasive (insertion of nasal prongs or catheters into the upper airway) (Frey and Shann 2003). The pros and cons of different methods have been reviewed (Rojas et al. 2009; Frey and Shann 2003).

Noninvasive methods require high oxygen flow and are therefore inefficient and uneconomical where resources are limited. Semi-invasive methods use lower flows and are therefore more appropriate where oxygen supplies are scarce. Some semi-invasive devices have an additional beneficial effect on lung function by producing positive end-expiratory pressure (PEEP) (Frey et al. 2001). This kind of PEEP production can also be effective in the management of apnoea (associated with prematurity or with bronchiolitis) (Sreenan et al. 2001).

Problems associated with oxygen delivery systems include dislodgement of nasal prongs and obstruction of catheters. Hypercapnoea (high levels of carbon dioxide in the blood) can result from inadequate flows through head boxes or face masks that allow build-up of carbon dioxide. Nasopharyngeal (N-P) catheters, and to a lesser extent nasal catheters, can obstruct airways or cause bleeding (Muhe and Weber 2001). Uncontrolled high PEEP production associated with inappropriately high oxygen flows through prongs or catheters may lead to gastric distension or pneumothorax. To minimize such problems, flow at the end of delivery tubing should be checked regularly using a detachable flow meter or sensor.

20.2 Continuous Positive Airway Pressure (CPAP) Systems

20.2.1 Bubble-Continuous Positive Airway Pressure (Bubble-CPAP)

A system of CPAP will be available in some hospitals but is only appropriate to use when basic, reliable, oxygen systems (described above) are in place, where staff are adequately trained and close monitoring is assured. CPAP delivers PEEP with a variable amount of oxygen to the airway of a spontaneously breathing patient to maintain lung volume during expiration. CPAP decreases atelectasis (alveolar and lung segmental collapse) and respiratory fatigue and improves oxygenation. Bubble-CPAP is an appropriate method for delivering CPAP and has been used successfully in some referral hospitals in developing countries (Koyamaibole et al. 2006). The bubble-CPAP system consists of three components:

1. Continuous gas flow into the circuit: CPAP requires a source of continuous airflow (often an air compressor). The gas flow rate required for generating CPAP is usually about 5–10 l/min. This alone can generate CPAP with a fraction of inspired oxygen (FiO_2) of 21 %, but many neonates require some supplemental oxygen. Therefore, bubble-CPAP also usually requires an oxygen blender that connects an oxygen source (cylinder or concentrator) with the continuous airflow to increase the FiO_2 .
2. A nasal interface connecting the infant's airway with the circuit: short nasal prongs are generally used to deliver nasal CPAP. These must be carefully fitted to minimize leakage of air (otherwise CPAP will not be achieved) and to reduce nasal trauma.
3. An expiratory limb with the distal end submerged in water to generate end-expiratory pressure: in bubble-CPAP the positive pressure is maintained by placing the far end of the expiratory tubing under water. The pressure is adjusted by altering the depth of the tube under the surface of the water.

20.2.2 High-Flow CPAP

There is some recent experience with a simpler method of delivering CPAP to newborns using high gas flow (up to 6–8 l/min) through normal nasal prongs. Although PEEP can be generated by this method, it is not as simple as dialling higher flows from an oxygen source such as a cylinder or concentrator; this would be very dangerous. This method requires highly effective humidification to prevent drying of nasal mucosa, which can lead to bleeding and nasal obstruction. A heated humidifier is necessary; an unheated cold water bubble humidifier would not provide adequate humidification.

High-flow CPAP also requires an oxygen/air blender. It is dangerous to give high-flow oxygen to a preterm baby as the fractional inspired oxygen achieved would be very high, increasing the risk of eye damage. Unlike with bubble-CPAP, with high-flow methods, it is not certain what pressure is being delivered, and there is a risk of pneumothorax and gastric distension. All methods of CPAP require careful monitoring.

20.2.3 CPAP/BiPAP Drivers for Noninvasive Respiratory Support

Devices are now available for delivery of CPAP or biphasic positive airway pressure for use via a face mask. These are covered elsewhere in the book but may be applicable to hospitals in developing countries. These devices are modest cost (less than \$1,000), but all have disposable circuits, and such recurrent costs can be difficult to maintain. Methods to clean and reuse CPAP and ventilator circuits need to be explored.

of child deaths will be preventable or treatable by simple measures, such as immunization, primary care and good quality, but basic, curative services in hospitals. In these situations it does not make sense to spend vast resources on intensive care in tertiary institutions to which only a small proportion of children will have access, when simpler and cheaper life-saving treatments are not available to a substantial proportion of sick children.

The main argument against providing intensive care in high-mortality areas is that this would divert scarce resources away from more effective, low-cost interventions. Following the principles of equity, countries and hospitals should ensure that highly cost-effective health interventions that will reduce mortality are available to the vast majority of children, *before* funding intensive care services.

There are, however, good practical and ethical arguments for providing selective postoperative intensive care services even where national or regional mortality rates are high. Many patients who have undergone surgery die for want of appropriate supportive care, including mechanical ventilation, in the first 24 postoperative hours. The World Health Organization suggests that facilities for intensive care should be available in any hospital where surgery and anaesthesia are performed and has published standards for intensive care units in large referral hospitals, district/provincial hospitals and small hospitals in developing countries (World Health Organization 2003). These standards outline conditions that should be able to be managed, procedures that should be able to be performed and personnel, drugs and equipment that are necessary. Where mechanical ventilation is available, there is a good basis for providing intensive care for some other selected nonsurgical conditions, particularly neuromuscular paralysis after snakebite, which is time limited and likely to result in a good outcome if appropriate supportive care is provided.

Pre-existing conditions for the development of highly specialized paediatric intensive care are good vaccine services, good-quality primary- and first-referral-level care, under-5 mortality rates less than 30 per 1,000 live births, availability

20.3 Mechanical Ventilation

Intensive care can best be defined as the provision of prolonged mechanical ventilation via an endotracheal tube and other expensive technology. When countries have child mortality rates above 30 per 1,000 live births, a major proportion

of transportation, good access for the majority of the population and sufficient human resources. Until these are achieved, acute hospital clinical care should focus on improving triage, emergency care, supportive care (including oxygen, nutrition and safe administration of intravenous fluids), monitoring, discharge planning and follow-up, and not on mechanical ventilation or other high-technology interventions. These priorities are outlined in the *WHO Pocket book of hospital care for children* (World Health Organization 2005) and are the principles of high-dependency care.

20.4 Respiratory Stimulants (Methylxanthines) as Adjuvants in Neonatal and Infant Practice

Some medications (methylxanthines) can treat and prevent apnoea in premature neonates. In some hospitals, equipment for bubble-continuous positive airway pressure (bubble-CPAP) by nasal prongs will be available and is useful for the management of respiratory distress in neonates for whom basic support with oxygen is insufficient.

20.4.1 Methylxanthines

Aminophylline, theophylline and caffeine are methylxanthines and have several effects on the respiratory system. These include stimulation of the respiratory centre in the brain, and diaphragm contraction. There is encouraging evidence that in premature neonates with apnoea, aminophylline and caffeine are highly effective. These drugs may be more effective than continuous positive airway pressure (CPAP) in preventing the need for mechanical ventilation (Henderson-Smart et al. 2001) and more effective than tactile stimulation in prevention of apnoea (Osborn and Henderson-Smart 2000). Caffeine is associated with fewer adverse events than aminophylline and is equally effective in the treatment of apnoea in premature newborns (Comer et al. 2001).

Most studies of methylxanthines have been conducted in preterm babies, where the predominant pathologies are hyaline membrane disease and apnoea of prematurity. Whether such respiratory stimulants are beneficial for the treatment of apnoea in term babies and older infants has not been established in controlled trials. Aminophylline has, however, been used effectively in young infants with apnoea due to acute viral bronchiolitis.

Essentials to Remember

- The need for oxygen therapy should not only be based on SpO₂ values or invasively measured PaO₂ values but on the question whether oxygen delivery is adequate for metabolic needs. However a SpO₂ value >90 % can be judged as sufficient.
- With any flow O₂ delivery system inappropriately high oxygen flows through prongs or catheters may lead to gastric distension or pneumothorax. To minimize such problems, flow at the end of delivery tubing should be checked regularly using a detachable flow meter or sensor.
- Bubble-CPAP or variable flow CPAP systems require an oxygen blender that connects an oxygen source (cylinder or concentrator) with the continuous air-flow in order to adjust the FiO₂.
- High-flow CPAP systems require a highly effective humidification to prevent drying of nasal mucosa, which can lead to bleeding and nasal obstruction. Therefore, such systems require a heated humidifier system since an unheated cold water bubble humidifier does not provide adequate humidification.
- Following the principles of equity, countries and hospitals should ensure that highly cost-effective health interventions such as invasive mechanical ventilation that might reduce mortality

are available to the vast majority of children, *before* funding such intensive care services. However, mechanical ventilation should be available in any hospital where surgery and anaesthesia are performed.

- Methylxanthines might be successfully used not only in newborns but also in bigger children for stimulation of the respiratory centre in the brain, and diaphragm contraction. These drugs may be more effective than continuous positive airway pressure (CPAP) only in preventing the need for mechanical ventilation.

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Part VI

Clinical Use of Conventional Modes of Ventilator Support

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The goal of mechanical ventilation is to provide or improve ventilation, oxygenation, lung mechanics, and patient comfort while minimizing complications. Traditionally, volume control modes have been favored in the pediatric population because of the ability to guarantee a preset tidal volume (V_T) and minute ventilation (V_E) enabling straight-

forward manipulation of ventilation in response to changes in the partial pressure of carbon dioxide in the blood (PaCO_2). However, during volume control modes, there is no guaranteed limit of peak airway pressure. This lack of limitation of airway pressure may result in high peak airway pressures associated with changes in the patient's compliance and resistance, causing alveolar over-distension and barotrauma. In contrast, pressure control ventilation (PCV) allows control, or limitation, of the peak inspiratory pressure (PIP) and inspiratory time (T_i) with no guarantee of V_T .

Due to the limits of volume control discussed above, increasingly, PCV is utilized as a protective lung strategy, particularly in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (Prella et al. 2002). In neonates, there is a growing acceptance of combining pressure control with synchronized intermittent mandatory ventilation (SIMV) to offer the advantages of pressure control and the synchronization of SIMV. Pediatric patients with ALI or ARDS have a higher proportion of diseased, collapsed, or consolidated lung regions that take a longer time to open, and thus may require a longer T_i . During PCV, the inspiratory pressure and time are set by the clinician, and the ventilator adjusts the inspiratory flow to achieve and maintain the set inspiratory pressure based on the compliance and resistance of the patient. Setting adequate T_i is essential in all of the pressure control-style modes to enable the preset pressure to reach both healthy and diseased lung units (Marik and Krikorian 1997).

Due to the identified disadvantages of volume- and pressure-controlled modes, dual control

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modes, which allow the clinician to set a volume limit breath during a pressure-controlled breath, have been developed to provide the benefits of both volume and pressure control while avoiding the shortcomings of single control modes. Dual control modes include complex closed-loop systems that switch between pressure control and volume control either within a single breath or between individual breaths based on measured patient characteristics. In the first sections of this chapter, we will discuss common control modes of ventilation including assist control (A/C), pressure control, and volume control. Our discussion will focus on the technical aspects of each mode and their advantages and disadvantages in neonatal and pediatric patients. In the subsequent sections, we will focus on dual control modes as an alternative to traditional control modes and finally a discussion of support modes.

21.1 Assist-Control Ventilation/ Intermittent Positive Pressure Ventilation

21.1.1 Principles

Assist-control ventilation, also known as patient-triggered ventilation and synchronized intermittent positive pressure ventilation, is a ventilator mode where every spontaneous inspiratory effort is assisted by a positive pressure breath triggered in synchrony. In the absence of spontaneous breathing efforts or if these are insufficient to trigger a mechanical cycle, the ventilator automatically initiates a “controlled” or backup ventilator rate of intermittent mandatory ventilation (IMV) type of breaths. The concept behind the assist-control modality is that it attempts to guarantee a baseline V_E by means of a targeted V_T along with a predefined respiratory rate (Mador 1994). In addition, the patient is given the opportunity to exceed this prescribed V_E , if he desires, through his own spontaneous breathing efforts. Thus, the ventilator will control ventilation to a certain level, but has the flexibility to enable the patient to exceed the set targets. The “control” targets can be volume (volume control), pressure (pressure control), or volume target with pressure titrated (volume control plus or pressure-regulated volume controlled).

Incorporation of the Ayre’s T-piece principle to neonatal ventilators enables maintenance of a continuous flow of gas in the breathing circuit (bias flow), which is used to generate pressure at the airway opening and to remove exhaled gases (Kirby et al. 1972). Partial restriction of the bias flow by an expiratory valve increases airway pressure to the set positive end-expiratory pressure (PEEP), which is aimed at maintaining a continuous distending pressure to prevent alveolar collapse and maintain lung volume. This is particularly important because the endotracheal tube bypasses the upper airway, which prevents the glottis closure mechanism for maintenance of lung volume. The expiratory valve further obstructs the bias flow at intervals determined by the set expiratory time (T_e). This produces a controlled increase in the pressure at the airway opening to the desired PIP for the set T_i .

Intermittent positive pressure ventilation (IPPV) is termed time-cycled pressure-limited ventilation. This mode of ventilation is more commonly referred as IMV, but is also referred to as conventional and controlled mandatory ventilation (both abbreviated as CMV). Intermittent mandatory ventilation became the main stay of neonatal ventilation and remains one of the most common modes of ventilation worldwide.

21.1.2 Inspiratory Flow Settings

In most neonatal ventilators, there is a single flow control setting during IMV, which is applied during both the inspiratory and expiratory phases, while in other devices there is a separate setting for the inspiratory flow. In many new ventilators, an airway pressure profile setting is used in addition or in lieu of the inspiratory flow rate setting. Flow during the inspiratory phase determines the airway pressure profile. At higher flow rates, the airway pressure rises more rapidly and reaches the set PIP earlier. A rapidly rising airway pressure profile (approaching a square waveform) produces an initially high flow of gas moving through the patient’s airway towards the distal portions of the lung. The patient’s inspiratory flow profile, which indicates the speed at which

the lung is inflated, is characterized by an initial peak that rapidly decays towards zero as the lung fills.

Higher inspiratory flow rates will also prolong the plateau of the airway pressure during which the lung is kept inflated before the set inspiratory phase ends. Although this increases mean airway pressure and may improve oxygenation by better alveolar expansion, high flow rates are usually avoided to reduce the risk of lung injury caused by the sudden expansion of air spaces. In contrast, a low inspiratory flow rate may be insufficient to reach the set PIP during a limited T_i and deliver a smaller V_T . This will occur in older generation ventilators that do not self adjust the inspiratory flow to reach the set PIP. Inspiratory flow rates in small preterm infants are usually maintained between 5 and 8 L/min, but these can be set at higher values for larger infants. In general, there is little data on the most adequate flow rate for different patient sizes or disease conditions.

The flow rate during the expiratory phase plays an important role in maintaining the PEEP level. An insufficient bias flow, set manually or automatically, can induce elastic loading during spontaneous breathing when the infant's inspiratory flow is higher than the bias flow. This can be recognized by a decline in the PEEP level below the set value or even below zero during each inspiration. In newer ventilators, a flow demand valve adjusts the flow to maintain the PEEP level constant during the changing demands induced by spontaneous breathing. The expiratory flow rate is also used to remove the exhaled gases that would otherwise remain in the circuit near the airway opening and possibly inhaled again.

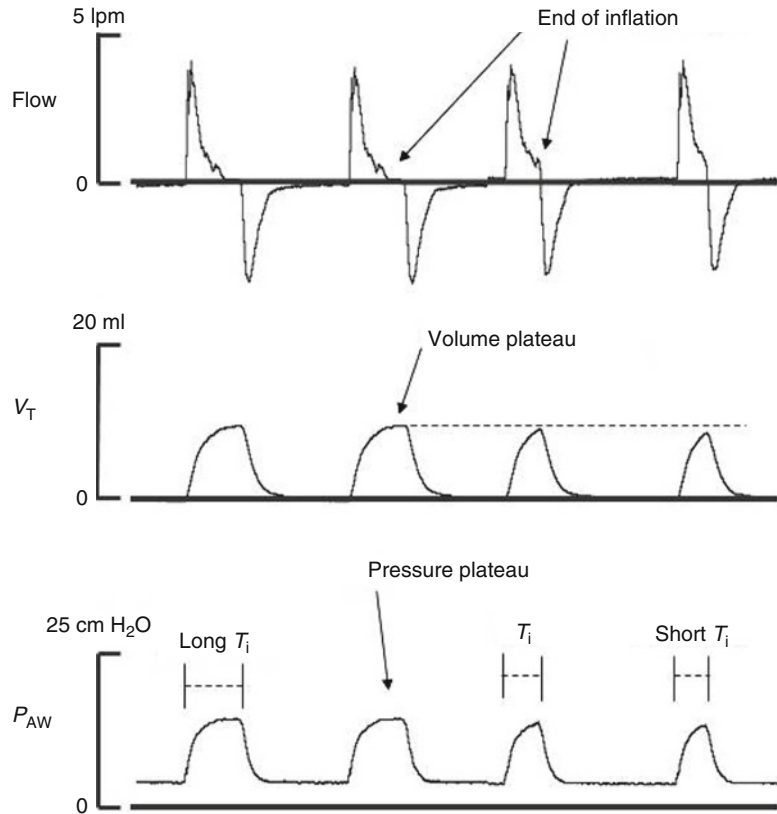
The work of breathing is minimized once the inspiratory flow rate reaches 65 Lpm in adults, and the patient is ventilated primarily in the control phase of the A/C modality (Ward et al. 1988). As the patient's spontaneous efforts become more frequent or dead space is added to the circuit, then the patient's work of breathing significantly increases and is difficult to attenuate with flow delivery in A/C ventilation (Marini et al. 1986). Historically, assisted breaths were facilitated with square wave flow patterns in the A/C form of ventilation. However, now they can be delivered by alter-

nate designs such as sine wave and accelerating and decelerating waveforms (Mador 1994). Perhaps more importantly, rates of flow can be adjusted during inspiration on many of the newer generation ventilators; however, the resultant flows created are still dependent on respiratory system compliance (Jolliet and Tassaux 2006; Richard et al. 2002). Nevertheless, the slope of pressurization which could result in less time for patient demand and less work of breathing is vastly improved in regard to the decelerating flow setting in the newer generation ventilators when evaluated in lung models (Richard et al. 2002).

21.1.3 Cycle Time Settings

The transition from inspiration to expiration is known as cycling. Typically, this occurs when instantaneous inspiratory flow (V'_{insp}) decreases to a predetermined fraction of peak inspiratory flow ($V'_{\text{insp}}/V'_{\text{peak}}$) which is referred to as an "expiratory trigger" (ET) (Jolliet and Tassaux 2006; Brochard 1994). Normally, cycling would coincide with the end of the patient's inspiratory demand. However, delayed cycling occurs when pressurization is extended by the machine into the patient's expiratory phase. This delayed cycling can lead to expiratory asynchrony and increased work of breathing (Jubran et al. 1995; Parthasarathy et al. 1998). On many ventilators, the cutoff value of ET is predetermined, usually at a default setting of 0.25; that is, the ventilator cycles when V'_{insp} has decreased to 25 % of V'_{peak} (Jolliet and Tassaux 2006). When airway resistance increases, the shape of the inspiratory flow curve changes. Hence, the 0.25 point will be reached later, which in turn increases the likelihood of delayed cycling (Jolliet and Tassaux 2006). Inspiratory time is managed to achieve the desired lung inflation. In A/C the ventilator cycles at the infant's spontaneous breathing frequency, therefore, long T_i is usually avoided to minimize the risk of insufficient time for exhalation that can lead to gas trapping or disruption of the breathing frequency. In some ventilators, the duration of the ventilator breath can be flow cycled and the set T_i becomes the duration limit.

Fig. 21.1 Recordings of flow, tidal volume (V_T), and airway pressure (P_{AW}) show the effects of a long T_i that prolongs the duration of the inspiratory phase and produces a volume plateau without achieving a gain in V_T . On the other hand, a short T_i does not allow for pressure equilibrium to be reached and full inflation is not achieved



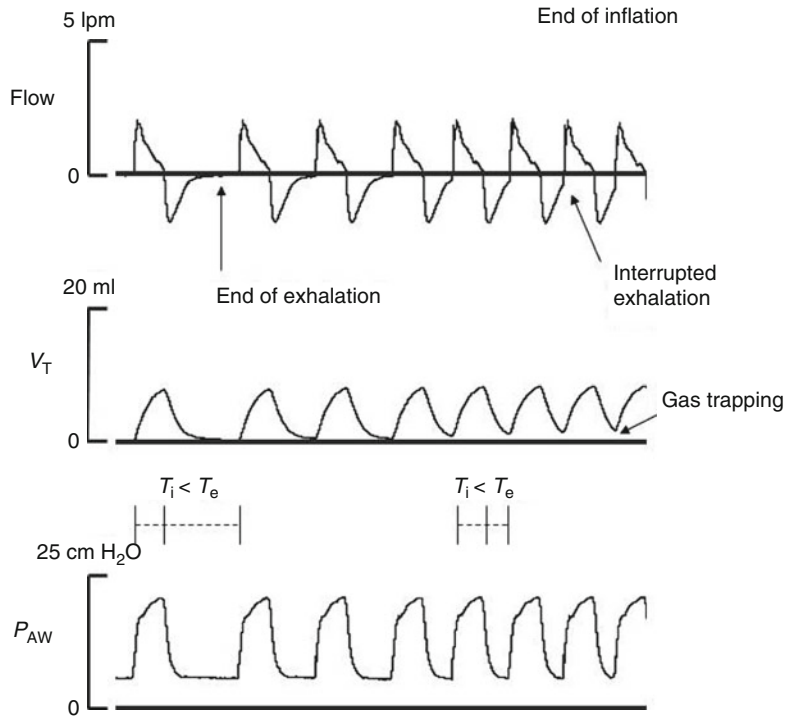
The increase in airway pressure during the mechanical inspiratory cycle produces lung inflation. T_i should be sufficiently long to allow complete lung inflation with the set PIP. Duration of the actual lung inflation does not depend on T_i except when T_i is too short. Lung inflation continues as long as the gradient produced by the increase in airway pressure relative to the alveolar pressure remains positive. As the lung inflates against the lung's recoil, the intrapulmonary pressure increases until it reaches equilibrium with the airway pressure and inflation ends. If T_i is insufficient, the inspiratory cycle ends before equilibrium and the delivered V_T is smaller. This is illustrated in Fig. 21.1.

The mechanical characteristics of the infant's respiratory system, compliance and airway resistance determine, the time constant of the respiratory system (their product), which varies during different phases of respiratory disease in preterm infants. In restrictive conditions such as RDS, lung compliance is low

(recoil is high with short time constant) and the pressure in the lung rises rapidly. Extending T_i may not increase V_T but only maintain a volume plateau. Thus, in cases of low lung compliance, an increase in PIP may be required to achieve the desired V_T , whereas a longer T_i may only prolong the inspiratory volume plateau. In obstructive conditions (high airway resistance, long time constant), the patient's inspired flow is reduced, which delays inflation and the rise in intrapulmonary pressure. The gradient between airway and the alveolar pressure persists longer, and equilibrium is reached later. In these cases, an insufficient T_i may not allow the desired V_T . In preterm infants presenting with RDS requiring mechanical ventilation, T_i is typically set between 0.25 and 0.4 s. Longer T_i and shorter T_e may result in gas trapping at very high ventilator frequencies as shown in Fig. 21.2.

The set T_e and T_i determine the ventilator frequency. Similarly to lung inflation, the actual duration of exhalation is not determined by T_e

Fig. 21.2 Recordings of flow, tidal volume (V_T), and airway pressure (P_{AW}) show the gas trapping produced when T_e is too short. Each new ventilator cycle interrupts and does not allow for a complete exhalation



except when T_e is too short. When T_e is too short, a new ventilator cycle interrupts exhalation resulting in gas trapping. This is more common with frequencies that result in T_e shorter than 0.5 s and when the time constant is prolonged. The longer time constant in obstructive conditions require careful adjustment of the ventilator rate to maintain the minimum T_e required for complete lung deflation.

21.1.4 Expected Physiologic Effects

Assist-control mechanical ventilation is designed to adequately eliminate carbon dioxide (CO_2) and deliver oxygen in order to meet metabolic requirements regardless of the patient's own breathing efforts (Mador 1994). Thus, the idea is to immediately avoid respiratory acidosis and to optimize aerobic metabolism. Respiratory acidosis is known to deepen sedation and cause "narco-sis" and can clinically cause stupor and coma (Kirsch and Jozefowicz 2002). On the other hand, arterial blood gas analysis needs to be carefully followed to avoid hyperventilation which could

result in hypocapnia and subsequent respiratory alkalosis which would lead to a "confusional" mental status (Cohen 2003). Moreover, sudden drops in CO_2 could result in stupor and coma as well, secondary to decreased cerebral blood flow and consequent ischemia (Faden 1976). In regard to oxygenation, metabolic alkalosis is known to shift the oxyhemoglobin disassociation curve to the left which results in less oxygen release to cells; this is known as the Bohr effect (Levitzky 1986).

The cardiac effects of CMV and IMV have been described in adults. In adults who have undergone aortocoronary bypass but otherwise have normal heart function, CMV decreased cardiac index and stroke volume compared to IMV suggesting a negative impact on preload from CMV. However, CMV was superior in patients with poor left ventricle function due to the observation that both pulmonary artery pressures and right atrial pressures increased during IMV indicating that higher metabolic demands were imposed in the setting of poor reserve (Mathru et al. 1982). Nevertheless, the negative cardiac effects of IMV in patients with poor ventricular function was ame-

liorated with the application of 5 cmH₂O PEEP (Mathru et al. 1982). This experience was corroborated by another group looking at the effects of PEEP at different ranges of pulmonary artery wedge pressures (PAWP) where there was a tendency for improvement in cardiac output with PEEP even at higher PAWPs (Grace and Greenbaum 1982). An approach called phasic high intrathoracic pressure support in adult patients in shock states (e.g., septic shock and cardiac infarction) where patients had their chest walls and abdomens binded resulted in improvements in cardiac output that was thought to be a result of decreasing left ventricular afterload (Pinsky and Summer 1983). For further details on cardiopulmonary interactions, see Part XVIII, Chap. 53.

21.1.5 Clinical Experience, Advantages, and Limitations

21.1.5.1 In the Neonatal Patient

Assist control can be used in both the acute and weaning phase of respiratory failure. In A/C, adjustment of PIP is primarily aimed at providing adequate V_T . Following the initial phase of respiratory failure, PIP should be gradually weaned by targeting 3–5 mL/kg as lung mechanics improve and the spontaneous inspiratory effort contributes more to the generation of V_T of the assisted breath. The backup ventilator rate is particularly important in preterm infants with inconsistent respiratory drive to avoid hypoventilation during apnea. However, a backup rate that is near or above the infant's spontaneous rate can take over ventilation by inhibiting the spontaneous respiratory drive.

Intermittent mandatory ventilation is used during the acute phase of respiratory failure as well as during the weaning and chronic phases of respiratory disease. During IMV, the total V_E is determined by the V_T generated by the ventilator and the cycling rate plus the contribution of spontaneous breathing. As the ventilator PIP and rate are decreased, the infant's inspiratory effort plays a larger role in the maintenance of ventilation. Inconsistency of the infant's respiratory drive

resulting in periods of absent spontaneous breathing, a respiratory effort insufficient to produce an adequate V_T , or significant mechanical loads imposed on the respiratory pump by the underlying lung disease often prolong the course of IMV. In general, V_T 's in the range of 3–5 mL/kg are considered appropriate in the neonate with lung disease. Ventilator rate is adjusted depending on spontaneous breathing and range of arterial CO₂ tension (PaCO₂) considered adequate. This is usually 40–50 mmHg, although higher PaCO₂ levels are often tolerated to facilitate weaning in infants with chronic lung disease.

The management of the ventilator settings during IMV is relatively simple which is particularly appealing to many clinicians and may be the reason why IMV became the mainstay in many neonatal intensive care centers. In older IMV devices, volume monitoring was not available and PIP was adjusted based on sufficient chest expansion and blood gas status. Inadequate or excessive lung inflation, reduced ventilation that could lead to progressive atelectasis, and the occurrence of gas trapping could not be identified whereas in newer ventilators graphic V_T monitoring can be used for PIP titration to maintain V_T within the desired range.

Asynchrony between the ventilator and the infant's spontaneous breathing is frequently observed during IMV. Ventilator cycles of fixed T_i and T_e can occur at different time points of the spontaneous breath. Spontaneous breathing frequency and duration of spontaneous inspiration and exhalation in preterm infants are very variable, which contributes to the asynchrony (Greenough et al. 1983a, b, 1984). When the mechanical breath is delivered midway or near the end of the spontaneous inspiration, it often extends into what should have been exhalation. By activating stretch inhibitory reflexes, the additional lung inflation or prolonged volume plateau produces an inspiratory hold and can limit the spontaneous respiratory rate. This could increase V_T above that generated by the spontaneous inspiration resulting in greater risk for volutrauma. A mechanical breath delivered during the spontaneous expiratory phase can, by the

same mechanism, prolong its duration and in some instances cause the infant to actively exhale against the positive pressure, which can lead to marked intrathoracic pressure swings. This ventilator asynchrony during IMV has been associated with air leaks and increased risk of intraventricular hemorrhage (IVH) (Perlman et al. 1983; Stark et al. 1979; Greenough and Morley 1984).

Assistance of every spontaneous inspiration in A/C produces a reduction in breathing effort compared to modes such as IMV or SIMV that assist only some spontaneous breaths (Hummler et al. 1996a; Kapasi et al. 2001). Therefore, many believe A/C prevents fatigue and produces a better V_T to dead space (V_D) ratio than the V_T produced by spontaneous breaths in IMV or SIMV. In randomized clinical trials, A/C was shown to facilitate weaning and reduce the duration of mechanical ventilation compared to IMV, but these differences were not observed when compared to SIMV (Chan and Greenough 1993, 1994; Donn et al. 1994; Baumer 2000; Beresford et al. 2000; Dimitriou et al. 1995). In A/C, PIP should be titrated carefully because an excessive V_T can lead to periods of hyperventilation with inhibition of spontaneous drive and apnea with the backup ventilator rate. On the other hand, if PIP is too low, ventilation may be insufficient during periods of apnea when the backup ventilator rate only delivers breaths of small V_T . Autocycling due to leaks around the endotracheal tube and water condensation in the circuit are common. None of the currently available ventilators have an actual upper cycling rate limit in A/C; therefore, autocycling is more serious in A/C than with SIMV because of the potential risk for hyperventilation leading to hypocapnia or gas trapping and inhibition of the spontaneous respiratory drive. Mechanical cycles with a T_i that exceed what is required for lung inflation or the duration of spontaneous inspiration are frequently observed in preterm infants (Dimitriou et al. 1998). Because these cycles are delivered at every spontaneous inspiration, they can disrupt spontaneous breathing pattern (Beck et al. 2004; Upton et al. 1990).

21.1.5.2 In the Pediatric Patient

The assist-control modality is used in pediatric patients who are either experiencing or recovering from deep sedation or anesthesia. Furthermore, the mode is used when supporting children with lung disease that requires moderate ventilator settings. Moderate ventilator settings defined as parameters used to support patients who generate PIP of 22–26 cmH₂O while delivering 6–8 mL/kg of V_T (maximum of 350 mL). Ideally, a patient considered a candidate for extubation should generate a PIP less than 22 cmH₂O while creating a V_T less than 8 mL/kg (maximum of 350 mL), a PEEP of 5 cmH₂O and an oxygen source of less than 40 % with an intact respiratory drive, ability to protect his airway, control his secretions, and exhibit easy work of breathing (e.g., no diaphoresis, tachycardia, or persistence of condition that resulted in intubation). The advantage of A/C ventilation is that the practitioner can continue to support patients with relatively poorly compliant lungs while allowing them to still breathe spontaneously. Potentially, analgesic and sedative requirements can be decreased if the ventilator's inspiratory demand mechanism operates with a high fidelity. The limitations of the A/C mode is that while the intention is to allow patients to breathe above the ventilator settings if desired, there may still be considerable pressures delivered by the ventilator that can be uncomfortable for the patient. Thus, some patients will not tolerate decreases in their analgesics or sedatives. Positive pressure ventilation in general may be detrimental in patients who are hemodynamically unstable with decreased intravascular volume and have tenuous pulmonary hypertension and increased intracranial hypertension.

21.2 Synchronized Intermittent Mandatory Ventilation

The idea of IMV was first described in the mid-1950s by Bjork and Engstrom (1955). This form of ventilation was successfully implemented in pediatric practice by Kirby and colleagues in the

management of infants with respiratory distress (Kirby et al. 1971, 1972; Kirby 1977). Synchronized intermittent mandatory ventilation is a mode of ventilator support in which a preset number of breaths (mandatory) are delivered over time (usually over a minute) and are targeted to a specific parameter [e.g., V_T (volume control) or pressure control] in a given breath cycle (typically 1 min). During SIMV, the mandatory breaths are either patient initiated or ventilator initiated. Furthermore, patients can initiate additional breaths if they desire above and beyond the set number prescribed. The principle difference in SIMV compared to other ventilator modalities where patients can initiate breaths is that in SIMV, the patient can breathe spontaneously and control the depth of his breaths. Classically, this mode was designed to “synchronize” a patient’s breathing effort with a ventilator’s response of support, but this is now a feature of other modes of ventilation as well (American Association for Respiratory Care 1992).

In SIMV, synchronous triggering is achieved by opening consecutive time windows where a mechanical breath is triggered by the first spontaneous inspiration in every new window. In the absence of spontaneous breathing, a mandatory mechanical breath is delivered at the end of the window. In this way, the interval between mechanical breaths is not constant as in IMV, but the total number of mechanical breaths delivered per minute is preset and constant. In SIMV, synchronous delivery of the mechanical cycle with the spontaneous inspiratory effort produces a greater transpulmonary pressure which results in an often larger and more consistent V_T compared to IMV cycles delivered at different points of the spontaneous breath as in IMV.

Various methods of synchronization have been used in neonatal ventilation. These include the Graseby pressure capsule that detects outward motion of the abdomen during inspiration, esophageal pressure balloon to detect negative deflection during inspiration, thoracic respiratory impedance, changes in airway pressure produced by spontaneous inspiration, and flow sensors that detect gas flow produced during spontaneous

inspiration. Most new generation ventilators utilize flow sensors for breath triggering in preterm infants. This is due to the greater sensitivity of these devices compared to other methods (John et al. 1994; Nikischin et al. 1996; Hummler et al. 1996b; Dimitriou et al. 2001). Flow sensors also allow monitoring of V_T and V_E produced by synchronized mechanical breaths and unassisted spontaneous breaths. Nonetheless, flow sensors have limitations related to autocycling due to leaks around uncuffed endotracheal tubes used in the neonate, or water condensation artifacts, and increased dead space (Figueras et al. 1997; Claire et al. 2003).

21.2.1 Pressure and Flow Triggering

The SIMV mode is designed to deliver a set amount of breaths as dialed into the ventilator. In addition, the patient can trigger breaths as sensed by the ventilator’s demand mechanism. Inspiratory efforts are typically sensed by either a pressure-triggered (PT) or flow-triggered (FT) mechanism. The PT mechanism detects a fall in pressure, whereas the FT strategy senses a change in flow before delivering a breath (Sassoon 1994). Consequently, the operator must set a threshold sensitivity in order for either a flow or PT breath to be delivered.

In regard to patient comfort, the work of breathing has been shown to be improved utilizing flow triggering in adults receiving either continuous positive airway pressure (CPAP) or SIMV (Branson et al. 1994; Sassoon et al. 1994). This is a characteristic of the efficiency of patient-ventilator interaction as well as the flow delivery attributes (e.g., bias flow which provides some pressure support prior to breath sensing compared to the pressure trigger mechanism) (Sassoon et al. 1994). In contrast, no difference in the work of breathing was appreciated by other investigators evaluating FT and PT in adults receiving pressure support (Goulet et al. 1997). In the SIMV mode in children, no significant decrease in the work of breathing was seen in spontaneously breathing subjects using the FT by

Thiagarajan et al., though these patients were deemed ready to extubate at the time of the assessment (Thiagarajan et al. 2004). Thus, the effects of PT and FT may not be discernable until managing children with lung disease.

The management of SIMV is in many aspects similar to that of IMV during the different phases of respiratory disease. Flow settings during SIMV, as in IMV, should be sufficient to maintain PEEP and flush exhaled gases during the mechanical expiratory phase and enable generation of the desired PIP within the allotted T_i .

Cycle time settings during SIMV are for the most part similar to those for IMV. However, because every mechanical cycle is synchronized with the spontaneous inspiration, insufficient trigger sensitivity (delayed triggered) or a too long T_i can prolong the cycle into the spontaneous exhalation phase in a consistent basis, whereas in IMV, these occur only in some of the mechanical cycles. Since V_T is more consistent and larger with SIMV, a slightly shorter T_i is often sufficient to achieve lung inflation.

Many ventilators provide the ability to cycle off the mechanical breath when inspiratory flow declines towards zero near the end of inflation or the spontaneous inspiration. This technique is coined flow cycling and consists of terminating the ventilator cycle when flow declines below a preset fraction of the peak flow measured during inspiration. A separate control is available in some ventilators by which the operator sets the fraction of the peak inspiratory flow at which inspiration ends. With this, the actual T_i setting becomes a maximum duration limit and the effective T_i is automatically adjusted during each breath.

21.2.2 Cycle Time Settings

Conceptually, the breathing cycle is partitioned into two phases; phase one is characterized by the delivery of the preset mandatory breath. Again in this phase, the patient can trigger the breath, but if he fails to, then the ventilator will deliver the breath before this phase ends. In the

second phase, only the patient can trigger a breath and oftentimes there is some support provided (e.g., pressure support) to lessen the effort required. Thus, the actual cycle time setting is determined based on the number of breaths that the practitioner wishes to have over a 1-min period. The number of breaths is used to divide 60 s (1 min) in order to define the “mandatory breath period.” For instance, if one wants a patient to be guaranteed at least 20 bpm, then this would result in a cycle time of 60 s divided by 15 or 4 s per cycle time. In other words, if a patient takes a breath at the beginning of the 4-s period, then he may take more breaths during the remaining time if he desires until the next 4-s window occurs. Nevertheless, if the patient does not initiate a breath within that 4-s period, then the ventilator will deliver a breath.

21.2.3 Expected Physiologic Effects

By far, the most anticipated physiologic effect of SIMV is the preservation of spontaneous breathing while minimizing the imposed work of breathing from the ventilator circuitry and demand valve mechanism by means of a responsive ventilator with a trigger feature that functions at high fidelity (Sanders et al. 2001). In addition, the ability to breathe spontaneously in this mode would enable the patient to augment their respiratory delivery to meet their metabolic demands if desired and perhaps direct airflow to areas that have better ventilator: perfusion ratios. Nevertheless, it is important to understand that despite the intent to allow the patient to breathe as much as tolerated, the subject is still receiving positive pressure ventilation. Thus, certain congenital heart lesions that may benefit physiologically in regard to cardiac preload, afterload, or pulmonary blood flow from a negative pressure respiratory situation would not necessarily do better in the SIMV mode compared to other modes of positive pressure ventilation from a physiologic perspective.

21.2.4 Clinical Experience, Advantages, and Limitations

21.2.4.1 In the Neonatal Patient

Synchronized intermittent mandatory ventilation was one of the synchronized modes of neonatal ventilation that was more rapidly adopted in neonatal centers because it maintained the general management features of IMV. Synchronized intermittent mandatory ventilation is commonly used during the acute phase of respiratory failure throughout the weaning as well as chronic phases of respiratory failure in preterm infants. During SIMV, the infant's inspiratory effort contributes to the generation of V_T of the synchronized mechanical breath. Peak inspiratory pressure is gradually reduced as lung mechanics improve and the infant's contribution to maintain V_T increases. Tidal volume in the range of 3–5 mL/kg is generally considered adequate for the neonate with lung disease. In SIMV, total V_E is determined by the V_T of the assisted breaths and the ventilation produced by the non-assisted spontaneous breaths occurring between SIMV cycles. As the ventilator PIP and rate are decreased, the infant's inspiratory effort plays a larger role in the maintenance of V_E .

In the acute phase of respiratory failure, SIMV rate ranges between 40 and 60 breaths per min (bpm) which is likely to assist almost every spontaneous inspiration. The ventilator rate is gradually weaned as the spontaneous breathing becomes more consistent to achieve acceptable levels of PaCO_2 depending on the condition of the infant. In most cases, acceptable PaCO_2 levels range between 40 and 50 mmHg, but in infants with chronic lung disease higher PaCO_2 are often tolerated.

In preterm infants, SIMV produces a more consistent and larger V_T compared to IMV which leads to improved gas exchange and a more efficient ventilation requiring a lower spontaneous breathing frequency (Bernstein et al. 1996; Smith et al. 1997; Cleary et al. 1995). In clinical trials, SIMV has been shown to accelerate weaning, shorten mechanical ventilation, and reduce the incidence of severe bronchopulmonary dysplasia in infants weighing <1,000 g at birth (Bernstein

et al. 1996; Chen et al. 1997). A recent report indicates less spontaneous fluctuations in oxygenation during SIMV vs. IMV (Firme et al. 2005).

Inadequate function or setting of the synchronization mechanism can lead to delay or lack of triggering and autocycling during SIMV. Delayed triggering with respect to the onset of the spontaneous inspiration, usually caused by insufficient sensitivity of the trigger setting, can prolong the inspiratory phase and disrupt the breathing pattern (Beck et al. 2004). Lack of triggering during SIMV, which usually occurs when the spontaneous inspiration is not sufficient to reach the trigger threshold level, results in the ventilator cycling at the set mandatory rate as if the infant was supported in IMV. On the other hand, a too sensitive trigger setting or a continuous gas leakage can produce autocycling at the set ventilator rate, which also results in a ventilator pattern that resembles IMV.

Weaning of the ventilator rate during SIMV can be adjusted depending on the infant's ability to provide a compensatory increase in his/her spontaneous ventilation. Some argue that not assisting spontaneous breaths between synchronized cycles is counterproductive due to the increased work of breathing, while others suggest this may increase diaphragmatic fitness and eventually facilitate extubation and that exposure to fewer ventilator cycles may reduce the risk of lung injury.

21.2.4.2 In the Pediatric Patient

In the pediatric intensive care unit (PICU), a myriad of ventilator modalities have been used in the management of critically ill children. In one survey, the majority of PICUs in the UK utilized SIMV in the management of this population though no well designed randomized controlled trials corroborated the effectiveness of this mode (Manczur et al. 2000a). Following the purported benefits of SIMV in neonates, studies were initiated looking at the role of SIMV in the PICU (Chan and Greenough 1994). In the UK study looking at 40 children (ages 1 month to 17 years), the work of breathing as measured by the pressure time product (PTP), PTP was improved in

the group receiving SIMV compared to CPAP (Manczur et al. 2000a).

21.2.5 SIMV for Ventilator Weaning

Successfully weaning children within the PICU depends on reversing the physiologic process that mandated mechanical ventilation, restoring or preserving the subject's respiratory drive, and counteracting imposed work of breathing from supportive devices (Sanders et al. 2001; Khan et al. 1996). The use of SIMV for weaning was revolutionized by Downs and his colleagues in adult patients (Downs et al. 1973). Initial reports of the comparison of SIMV over T-piece trials in the weaning of adults did not demonstrate one strategy to be better than the other (Hastings et al. 1980; Tomlinson et al. 1989). Furthermore, Brochard et al. demonstrated in intubated and mechanically ventilated adults that there were significantly lower weaning failures using pressure support ventilation compared to either T-piece trial or SIMV (Brochard et al. 1994). A formidable challenge in studying weaning strategies in children is the need to establish sufficient power for significance which often requires multicenter coordination and recruitment. In children, over 25 % of the patients are intubated and placed on mechanical ventilation for non-pulmonary specific causes such as upper airway obstruction or cyanotic heart disease (Randolph et al. 2003). Furthermore, studies meticulously designed to address lung specific causes of mechanical ventilator needs in children typically result in the exclusion of two thirds of the PICU population (Randolph et al. 2002). In a study of 70 children intubated for at least 48 h, there was no difference in weaning between a group that received IMV and another group that received SIMV and pressure support (de Moraes et al. 2009). Nevertheless, it has been shown that when evaluating children within the PICU who were clinically judged to be ready for weaning, the work of breathing was lower in patients receiving SIMV compared to CPAP (Smith et al. 1997). The clinical success of weaning children occurs over a very brief period of time since most

patients are weaned and extubated over 48 h in most PICUs compared to the longer durations in adults (Randolph et al. 2002). Thus, metrics used to assess effectiveness of weaning from mechanical ventilation in the pediatric population may need to be revised, such as looking at ventilator costs, personnel workload effects, and user input requirements in addition to physiologic and clinical factors.

21.3 Pressure Control Ventilation

During PCV, a pressure-limited breath is delivered during a preset T_i at the preset respiratory rate. The V_T is determined by the preset pressure limit. The flow waveform is always decelerating in pressure control. Gas flows into the chest along the pressure gradient. As the alveolar pressure rises with increasing alveolar volume, the rate of flow drops off (as the pressure gradient narrows). The pressure is maintained for the duration of inspiration.

Pressure-controlled ventilation has several advantages. The higher initial flow associated with pressure-controlled ventilation more easily meets the patient's flow demands. The PIP during pressure-controlled ventilation is less compared to volume-controlled ventilation for the same V_T . During pressure-controlled breaths, the distribution of ventilation may be more even in a lung with heterogeneous mechanical properties. Pressure control is also useful in patients with an air leak; although volume is lost through the leak, the ventilator will continue to attempt to maintain the airway pressure for the duration of the inspiratory phase.

Pressure-controlled ventilation also has several disadvantages. Pressure control ventilation does not guarantee V_E and therefore, requires closer observation by the healthcare provider. The delivered V_T will change as the patient's lung mechanics or effort changes. Worsening of the patient's compliance or the resistance results in hypoventilation and hypoxia. Conversely, an improvement in patient compliance or increasing patient effort can lead to a higher V_T with alveolar overdistension (volutrauma).

21.4 Volume Control Ventilation

In volume control ventilation, the ventilator delivers a preset V_T with a constant flow during a preset T_i at the preset respiratory rate. Airway and alveolar pressures are dependent variables and will rise or fall depending upon changes in lung mechanics or patient effort.

Volume-controlled ventilation includes the following advantages. The clinician has control over V_E and CO_2 clearance, provided there is only a small leak around the endotracheal tube; also, ventilator-induced lung injury due to alveolar overdistention (volutrauma) can be less.

Volume control ventilation also has the following disadvantages. The constant flow type of breath delivery in volume-controlled ventilation may not meet patient demand and may cause asynchrony between the patient's breathing efforts and the ventilator leading to an increase in sedation. The PIP is higher in volume-controlled ventilation compared to pressure-controlled ventilation for the same V_T .

21.5 Five Hybrid Techniques

Hybrid techniques, also described as dual controlled ventilation, are modes that allow the clinician to set a volume target while the ventilator delivers a pressure-controlled breath. Dual control of the breath in these hybrid modes is designed to be either intrabreath (within a breath) or interbreath (breath to breath). Examples of dual control intrabreath modes are volume assured pressure support and pressure augmentation. In these modes, the ventilator switches from pressure control to volume control during a single breath. Examples of dual control interbreath modes are pressure-regulated volume control (PRVC), volume guarantee (VG), adaptive pressure ventilation (APV), autoflow, and variable pressure control. In these modes, the pressure limit is increased or decreased automatically to maintain a clinician selected target volume.

Frequently used hybrid modes are discussed in the following sections.

21.5.1 Pressure-Regulated Volume Control and Volume Guarantee

Pressure-regulated volume control mode is one of inspiratory pressure regulation, available on the Servo-i ventilator (Maquet, Solna, Sweden), with the goal of providing the flow example of adaptive targeting synchrony of set point pressure control with the V_T assurance of set point volume. A common concern with set point is it cannot guarantee a minimum V_T in the face of pressure control ventilation with changing lung mechanics or patient efforts. Pressure-regulated volume control was one manufacturer's solution to this problem. Other manufacturers have described similar modes named adaptive pressure ventilation, autoflow, volume control +, or variable pressure control, all of which are dual control breath-to-breath modes.

In these modes, the operator inputs a target V_T and the controller manipulates the flow within a breath to control the inspiratory pressure to a constant value (pressure control). Between breaths, the inspiratory pressure is automatically adjusted by the ventilator to achieve the target volume. Adaptive pressure targeting has been used for both mandatory and spontaneous breaths in the various modes that use this scheme as described above.

In PRVC, there is a variable decelerating flow pattern with breaths time cycled. During PRVC, the pressure and volume are regulated. Thus, all breaths are volume targeted with pressure adjusted to reach that volume target. The proposed advantage of this mode is a constant minute ventilation and V_T with automatic weaning of the pressure limit as the patient's compliance improves.

Volume guarantee (CG) is slightly different from PRVC given that the flow pattern is constant. In such, it is a modification of pressure-limited ventilation targeting volumes in a time- or

flow-cycled mode. Volume guarantee is an option available on the Babylog 8000+, the newer VN 500 (both from Draeger Medical, Lübeck, Germany), as well as the Leoni Plus (Heinen+Löwenstein GmbH, Bad Ems, Germany). Recently, a version of this mode has been implemented on the Avea ventilator (CareFusion, San Diego, CA), the Fabian (Acutronic, Hirzel, Switzerland), and the SLE 5000 (SLE Limited, South Croydon, England), but there are no published studies as yet regarding the performance or effectiveness of these volume guarantee or also called volume-targeted modes as implemented on these device. Volume guarantee may be combined with any of the standard ventilator modes (A/C, SIMV, and pressure support ventilation (PSV)). With this mode, the microprocessor compares the *exhaled* V_T of the previous inflation measured by a hot wire anemometer at the airway opening to the set target and adjusts the working pressure up or down to reach the target V_T . Exhaled V_T is used to adjust inflation pressure because it more closely approximates the volume of gas that had entered the patient's lungs in the presence of endotracheal tube leak, a common problem in newborns with uncuffed endotracheal tubes (Bernstein et al. 1995). In general, the algorithms limit the pressure increment from one inflation to the next to avoid overcorrection that could lead to excessive V_T delivery and oscillations in the system. This constraint and the use of exhaled V_T of the previous inflation results in a short delay before the delivered V_T returns to the target value after a rapid change in compliance or patient inspiratory effort. Inflation triggered by the infant (assisted breaths) and un-triggered mechanical inflations are each controlled by a separate algorithm to minimize fluctuations in V_T in preterm infants with irregular respiratory effort. For the Draeger devices, the following additional control concepts apply during volume adaptation in response to a rapid change in compliance or patient's respiratory effort. To minimize the risk of delivering an excessively large V_T , the microprocessor opens the expiratory valve and terminates gas delivery if the V_T during inflation exceeds 130 % of the

target. The algorithm is designed to make slower incremental adjustment for low V_T and more rapid adjustment for excessive, potentially dangerous V_T . Therefore, the term "guarantee" is somewhat misleading, because as with all volume-targeted modes, the V_T fluctuates around the target value in spontaneously breathing infants who are constantly perturbing the equilibrium with their variable respiratory effort. Nonetheless, the V_T has been documented to be much less variable with than without VG (Keszler and Abubakar 2004a). *Warning:* The inflation pressure will default to the PIP limit if the flow sensor is temporarily removed (such as around the time of surfactant administration or delivery of nebulized medication), if its function is affected by reflux of secretions or surfactant, or if it malfunctions for any reason. Manual inflation (activated by depressing a key on the front panel) also uses the set PIP limit.

Automatic reduction of inflation pressure in response to improved lung compliance and increased patient respiratory effort makes VG a "self-weaning" mode. Reduction of inflation pressure occurs in real time as compliance and respiratory effort improve, rather than intermittently in response to blood gas measurement. Because of the use of exhaled V_T to regulate inflation pressure, VG is more tolerant of endotracheal tube leak than volume-targeted modes that measure V_T during inflation. Nonetheless, VG or volume-targeted ventilation becomes impractical in the presence of leak that substantially exceeds 30 %, because the V_T measurement increasingly underestimates the actual delivered V_T . A large leak that cannot be corrected by repositioning the infant/endotracheal tube indicates that the tube has become too small due to stretching of the trachea and larynx from continuous cyclical positive pressure. The problem can usually be corrected by re-intubating the infant with a larger endotracheal tube. The newer VN 500 overcomes this problem by giving the user the option of using a leak-compensated V_T that effectively corrects for leaks of up to 60–70 %.

Table 21.1 Clinical guidelines specific to the VG mode as implemented on the Dräger devices

Initiation
Ideally, VG should be initiated as soon as possible after intubation because this is the time when the most rapid changes in lung mechanics are likely to occur
There are two basic ways to initiate VG. If the patient is already mechanically ventilated with PLV and has good gas exchange, it is reasonable to select a target V_T based on the observed V_T during PLV and then increase the PIP limit by about 20 % from baseline to allow the microprocessor to adjust the PIP up and down as needed
The alternate method when starting VG as the initial mode is to select the starting V_T based on the particular patient's characteristics and select the inflation pressure limit 3–5 cmH ₂ O above the level estimated to be sufficient to achieve a normal V_T in that infant
If the target V_T cannot be reached with this setting, the pressure limit should be increased until the desired V_T is generated, but excessive pressures must be avoided. It is important to make sure the endotracheal tube is not kinked, malpositioned in the mainstem bronchus, or obstructed on the carina. Significant volutrauma and/or air leak could result from failure to recognize single-lung intubation with any modality of VTV
The usual starting target V_T for infants 500 g–1,000 g is 4.5–5 mL/kg during the acute phase of RDS. Larger infants with RDS only need 4–4.5 mL/kg, but infants with MAS may require slightly larger V_T (5–6 mL/kg) due to the larger alveolar dead space related to heterogeneous inflation and air trapping (American Association for Respiratory Care 1992)
All of these values were derived from VG use in combination with A/C or PSV. If using SIMV at rates <40 the V_T targets may need to be slightly larger to achieve the same minute ventilation
Larger tidal volumes (as much as 6–8 mL/kg) are needed in older infants with chronic lung disease because of increased anatomic and physiologic dead space as a result of dilated large airways and wasted ventilation resulting from air trapping and heterogeneous aeration (Stark et al. 1979)
The PIP should be set about 20 % higher than the working pressure (the PIP currently needed to deliver the target V_T) to give the device adequate room to adjust PIP but low enough for optimal safety
The working pressure, which is the true reflection of the level of support the infant is receiving must be recorded, in addition to the PIP limit
Caution should be exercised when administering surfactant during VG. Under normal circumstances the working pressure increases as needed in response to the transient small airway obstruction caused by surfactant and maintains normal gas exchange. However, if the ventilator senses complete ETT obstruction, it will drop inflation pressure midway between PIP limit and PEEP as a safety measure. If this is not recognized, significant deterioration may occur (Nikischin et al. 1996)
Subsequent adjustments
Subsequent adjustment to the target V_T can be made based on PaCO ₂ , persistent tachypnea, or signs of increased WOB. The usual increment is 0.5 mL/kg
Although adjustment is seldom necessary when the initial value is chosen carefully, it should be understood that the suggested V_T settings are only the typical values. Individual patients may have different needs, based on factors such as larger than normal physiologic dead space due to excessively high PEEP leading to overexpansion, the presence of metabolic acidosis (pH, not PaCO ₂ drives the respiratory control), or increased CO ₂ production, such as may occur with fever or sepsis
The PIP limit needs to be adjusted from time to time to keep the PIP limit sufficiently close to the working pressure (remember that inflation pressure will default to the PIP limit if the flow sensor is removed, malfunctions for any reason, or with “manual inflation”), but high enough to avoid frequent alarms. In most infants, keeping the pressure limit 4–6 cmH ₂ O above average working pressure is appropriate. <i>Note:</i> Ideally, when removing the flow sensor for significant periods, such as when nebulizing medications, the PIP limit should be adjusted to roughly match the average or recent working pressures
If the infant appears agitated, with episodes of spontaneous hyperventilation, optimize positioning, limit noise, and consider light sedation (avoid oversedation, with complete suppression of respiratory effort)
If the PaCO ₂ is too low despite V_T set at the low end of normal, make sure there is no substantial leak around the ETT (or make sure the leak-compensated V_T is being used with the VN 500). Other causes of hypocapnia may be agitation and low PEEP causing the infant to be tachypneic (shorten expiratory time) in an effort to maintain lung volume. In extremely small infants, PSV may lead to excessive tachypnea due to their very short time constant – A/C may be preferred in the first few days of life

Table 21.1 (continued)

If the infant has persistent tachypnea or is consistently breathing above the set V_T , the WOB will be excessive. Consider increasing the V_T target even if the PaCO_2 and pH are adequate. However, if the PaCO_2 is low and the respiratory rate is high, comfort measures or sedation may be indicated
If the low V_T alarm sounds repeatedly, increase the pressure limit to allow the device to reach the desired V_T . Repeated alarms suggest that there has been a change in lung mechanics or patient respiratory effort (e.g., atelectasis, pneumothorax, pulmonary edema, right mainstem bronchus intubation, patient becoming septic, respiratory depression from narcotics). This early warning system is an important benefit of the VG mode and should not be ignored, but it will not be effective if the PIP limit is set too high
If the pressure limit has to be increased substantially, verify that the V_T measurement is accurate (assess chest rise, obtain a blood gas), seek the cause of the change in lung mechanics (examine the patient, verify ETT position, obtain a chest x-ray and blood gas), and evaluate spontaneous respiratory effort
Weaning from mechanical ventilation
Weaning from VG <i>does not</i> require lowering of the target V_T , because the physiologic V_T does not decrease – what decreases is the pressure needed to generate that V_T
When the target V_T is set at the low end of the normal range (but generally not <4 mL/kg) and PaCO_2 is allowed to rise enough to have a pH <7.35 , weaning occurs automatically, as the infant should have a good respiratory drive and gradually takes over the work of breathing
For infants who have chronic lung disease, a higher V_T should be used even during weaning because of the increased physiologic dead space. Automatic weaning occurs as long as the pH is low enough to give the infant good respiratory drive
If the V_T is set too high, resulting in pH ≥ 7.4 , the baby will not have a respiratory drive and will not “self-wean.” Instead, the baby will become dependent on the ventilator due to lack of respiratory muscle training
If the set V_T is too low, there will be increased WOB with eventual respiratory deterioration. Working pressure at or near the level of PEEP indicates that the set V_T is below the infant’s physiologic need. If the infant is not tachypneic and without retractions, extubation is indicated. If the opposite is true, V_T should be increased to provide adequate support and avoid fatigue
To ensure good respiratory effort, sedation should be avoided during the weaning phase
If an infant appears to not be weaning as expected, despite apparently improving lung disease, try lowering V_T by 0.5 mL as long as blood gases are adequate and the work of breathing does not appear excessive.
If significant oxygen requirement persists, PEEP may need to be increased to keep mean airway pressure from falling excessively as PIP is automatically lowered. Failure to do so may result in atelectasis, worsening lung compliance, and failure of extubation
Most infants can be extubated when they consistently maintain V_T at or above the target value with delivered PIP <10 – 12 cmH $_2$ O (<12 – 15 cmH $_2$ O in infants >1 kg) with FiO_2 <0.35 and sustained respiratory effort
Observing the graphic display of the working PIP is helpful in assessing for periodic breathing (variable respiratory effort) and apnea that may presage failure of extubation. Lowering the backup rate of A/C or PSV to 20 bpm for a few hours may help unmask inconsistent respiratory effort

These guidelines are specific to the VG mode as implemented on the Draeger infant ventilators. Modes similar to VG exist on other devices, but each device functions differently and may respond to perturbations in a different way. Please consult the product literature of each manufacturer for specific clinical guidelines for their respective ventilators. Two publications specifically provide clinical guidelines for VG (Perlman et al. 1983; Kapasi et al. 2001)

21.5.1.1 Patient-Ventilator Interaction with Volume Guarantee and Volume-Targeted Modes

Volume guarantee achieves a very stable V_T in a paralyzed patient with a snugly fitting endotracheal tube, but this is not the usual situation in the newborn intensive care unit. With all forms of synchronized ventilation, the V_T that enters the infant’s lungs is the combined result of the negative inspiratory effort of the infant and the positive inflation

pressure generated by the ventilator. Because the preterm infant’s contribution to this transpulmonary pressure is highly variable and inconsistent, the V_T of a mechanically ventilated spontaneously breathing infant is extremely variable. A key concept to understand is that, if the infant consistently generates a V_T larger than the set target, the ventilator will reduce the inflation pressure all the way down to the level of PEEP. This situation occurs in infants who have a sufficiently strong respiratory

effort to achieve the V_T of their respiratory drive demands, and the V_T target is set below that infant's physiologic need. As a result, the infant receives little or no support from the ventilator, resulting in increased work of breathing and over time leading to fatigue, atelectasis, and worsening gas exchange.

Other important interactions can occur with agitation or with forced exhalation episodes. Especially during the recovery phase of lung disease, even small preterm infants, when agitated, are capable of spontaneously generating large V_T that may briefly exceed 20 mL/kg. Some extremely premature ventilator-dependent infants develop frequent episodes of forced exhalation, a sort of Valsalva maneuver (Dimaguila et al. 1997). The reason for this behavior is unclear, but it halts all gas flow for several seconds and is accompanied by desaturation and bradycardia. Because the forceful exhalation results in substantial loss of lung volume and fall in compliance, recovery usually takes several minutes. Similar loss of functional residual capacity occurs with endotracheal tube suctioning. Our group recently demonstrated faster recovery from these forced exhalation episodes and from suctioning of the endotracheal tube with VG compared to standard pressure-limited ventilation (Abubakar et al. 2006; Keszler and Abubakar 2004b). Though clearly helpful in reducing the impact of these perturbations, VG could not eliminate substantial fluctuations in delivered V_T . McCallion et al. identified an additional source of fluctuation in V_T targeting by VG (McCallion et al. 2005). She observed that in 3 % of breaths, expiration was briefly interrupted by what was presumed to be diaphragmatic braking by the infant, causing the microprocessor to misidentify this interrupted exhalation as a full breath and use only a part of the actual V_T to regulate the pressure for the next inflation (though the 3 cmH₂O incremental limit will prevent major overshoot). It is therefore important to understand the complexity of patient-ventilator interactions and recognize that even with volume-targeted ventilation, considerable variability of individual V_T is to be expected in the awake, spontaneously breathing infant.

21.5.1.2 Clinical Experience in Neonatal Patients

In neonates, the introduction of effective volume-controlled ventilation allows the clinician to limit delivered volume to minimize ventilator-induced lung injury. There is limited data, in neonates, about the use of dual control modes such as PRVC despite the potential advantages of these dual control modes. However, similar modes have been developed on neonatal ventilators to obtain comparable results. These modes are described as volume guaranteed modes which are pressure limited, volume targeted, and time or flow cycled.

Volume guarantee as implemented on the Babylog 8000+ has been studied more extensively than other modes of volume-targeted ventilation, but to date, all studies have focused on feasibility and short-term outcomes, rather than major long-term benefits. The publications are reviewed here in approximate chronologic order, pointing out the key findings and limitations.

Cheema et al. compared A/C with and without VG in a short crossover trial in 20 infants with acute RDS and separately studied SIMV with and without VG during the weaning phase in an additional 20 infants (Cheema and Ahluwalia 2001). Transcutaneous oxygen and CO₂ were similar, and in contrast to all other studies, there was no difference in the variability of V_T . The peak inflation pressure was lower during the VG periods. Both findings likely were an artifact of inappropriately limiting the PIP to the same level as during the pressure-limited periods, rather than allowing the PIP to fluctuate, as intended by the manufacturer, in order to achieve the target V_T .

In contrast to the previous study, we showed in a short-term crossover trial that VG, whether combined with A/C, SIMV, or PSV, led to significantly lower variability of V_T compared to A/C or SIMV alone and similar PIP (Abubakar and Keszler 2001). This difference is explained by the fact that in order to allow the device to effectively control V_T , the working pressure is adjusted both up and down by raising the pressure limit from the baseline period. The use of VG does not alter the relationship between PIP, compliance,

and V_T ; therefore, there is no reason to expect the PIP to be lower for the same V_T .

In a group of preterm infants recovering from acute respiratory distress, Herrera et al. (2002) showed that short-term use of SIMV + VG decreased mechanical support and enhanced spontaneous effort compared to SIMV alone while maintaining adequate gas exchange. The shift of the work of breathing to the infant resulted from a reduction of V_T to 4.5 mL/kg from the usual V_T of mechanical inflations on SIMV of about 6 mL/kg (Hummler et al. 1996a; Osorio et al. 2005). An almost complete shift of the work of breathing to the infant occurred when the target V_T was reduced to 3 mL/kg indicating that this value is too low. There was a reduction in excessively large V_T during both VG periods.

Olsen et al. compared 4-h periods of PSV + VG with SIMV alone in a crossover trial in 14 infants with mean gestational age of 34 weeks (Olsen et al. 2002). Gas exchange and dynamic compliance were similar during both periods. Minute ventilation and mean airway pressure were higher and end-expiratory volume was lower during PSV + VG compared to SIMV. The authors concluded that the use of PSV + VG could not be recommended, but this conclusion should be viewed with caution because of significant problems with study design, data acquisition, and interpretation (Keszler et al. 2003).

In the first randomized controlled trial of VG in preterm infants, we demonstrated that VG combined with A/C maintained PaCO_2 and V_T within a target range more consistently than A/C alone during the first 72 h of life (Keszler and Abubakar 2004a). We saw a 41 % reduction in V_T >6 mL/kg and a 45 % reduction in PaCO_2 <35 mmHg, demonstrating that excessively large V_T and hypocarbia could be reduced, but not completely eliminated with the use of VG.

Lista et al. randomly assigned 53 preterm infants with RDS to PSV alone or PSV + VG using set V_T of 5 mL/kg (Lista et al. 2004). Proinflammatory cytokine levels were lower in the tracheal aspirate of infants in the VG group. The duration of mechanical ventilation was 8.8 ± 3 days in the VG group compared to 12.3 ± 3 days with PSV alone (mean weighted difference

−3.5, CI: −5.13 to −1.87). Death, BPD, and pneumothorax trended lower, but the study was not powered to assess these outcomes. These data strongly support the hypothesis that VG may reduce ventilator-induced lung injury.

Nafday et al. (2005) compared SIMV to PSV + VG in a randomized study of 34 infants with RDS. Time to extubation (primary outcome) and other important clinical outcomes were not different, but this “pilot” study lacked adequate statistical power, and the original group assignment was only maintained for the first 24 h, likely negating any possible differences. Significantly fewer blood gases were needed in the VG group.

Abd El-Moneim et al. (2005) studied 25 premature infants in a double crossover study alternating between SIMV and PSV + VG. They noted similar oxygenation but significantly lower PIP and better infant-ventilator synchrony during PSV. Mean PaCO_2 values were similar, but more episodes of hypocapnia were seen during PSV + VG, likely because the V_T observed during baseline low rate SIMV was by design matched during the PSV period. The mean V_T of 5.9 mL/kg is consistent with the typical V_T observed during SIMV but is 30–45 % larger than what is normally used in PSV when each breath is supported.

To determine whether VG is more effective when combined with A/C or SIMV, Abubakar and Keszler studied 12 infants with mean birth weight of 679 ± 138 g in an 8-h crossover trial (Abubakar and Keszler 2001). As anticipated, V_T was more stable with A/C + VG, because during SIMV there are fewer volume-targeted breaths, and thus a slower adjustment of working pressure. During SIMV, the infants had significantly lower and more variable oxygen saturation (SpO_2) and more tachycardia and tachypnea. The 5 mL/kg V_T was identical by design, but significantly higher PIP was required during SIMV to achieve the same V_T . The tachypnea, tachycardia, and lower, more variable SpO_2 suggest that the infants were tiring during the SIMV period and contributing less spontaneous effort to the transpulmonary pressure by the end of the 2-h period when the measurements were obtained.

Dawson and Davies (2005) examined the relationship between V_T , V_E , and PaCO_2 in patients ventilated with SIMV+VG. They reported that 96.5 % of the blood gases during the first 48 h were within their acceptable range of 25–65 Torr when the V_T was set at a mean value of 4 mL/kg. More importantly, only 0.3 % of PaCO_2 values were less than 25 Torr.

Lista et al. randomly assigned 30 preterm infants <32 weeks gestation to receive A/C+VG ventilation with either 3 or 5 mL/kg target V_T (Lista et al. 2003). Bronchoalveolar lavage on days 1, 3, and 7 revealed an *increase* in proinflammatory cytokines in the lower V_T group, most likely because of atelectasis resulting from the combination of low V_T and low end-expiratory pressure of 3–4 cmH₂O that was used. An accompanying editorial points out the critical importance of using the open lung approach to ensure that the V_T is evenly distributed throughout the entire lung, not just a small proportion of open alveoli (Keszler 2006).

Dani et al. (2006) compared proinflammatory cytokines in 25 preterm infants approximately 1,100 g and 28 weeks gestation randomly assigned to receive PSV+VG or high-frequency oscillatory ventilation (HFOV) using a high lung volume strategy. There was no difference in survival, length of ventilation, or oxygen requirement. IL 8 and IL 10 levels were lower in infants receiving HFOV at the end of 4 days. The combination of PSV (short inflation time) and PEEP of only 3 cmH₂O would result in a low lung volume strategy on PSV+VG compared with optimal lung volume with HFOV. Mounting evidence shows that optimization of lung volume is key to lung protection, regardless of which ventilation mode is used. VG applied to a poorly inflated lung is unlikely to be optimally lung protective.

Polimeni et al. compared SIMV and SIMV+VG in a group of infants with frequent episodes of hypoxemia (forced exhalation episodes) during alternating 2-h periods of ventilation (Polimeni et al. 2006). When using target V_T of 4.5 mL/kg, no benefit was seen. In a second phase, 20 infants were studied using a target V_T of 6.0 mL/kg in. The frequency of hypoxemic episodes did not change, but with the V_T set at a level

more appropriate for low rate SIMV, the mean episode duration was shorter and the proportion of inflations with $V_T \leq 3$ mL/kg was reduced during SIMV+VG vs. SIMV alone. In work only presented as abstract, we have documented more rapid recovery from episodes of forced exhalation with A/C+VG and a target of 4.5 mL/kg compared to A/C alone.

Scopesi et al. compared SIMV to SIMV+VG, A/C+VG, and PSV+VG in a small crossover trial of ten preterm infants in the recovery phase of RDS (Scopesi et al. 2007). All VG combinations delivered V_T close to the target value. The mean variability of V_T from the set V_T was lower in A/C and PSV modes than in SIMV. In all VG periods, the PIP was much lower than with baseline SIMV because a V_T of only 3.5 mL/kg was used. These larger infants were able to generate adequate V_T on their own with little or no inflation pressure from the ventilator, but the low target V_T led to greater than usual variability in all the VG modes studied.

Cheema et al. studied the impact of VG on the incidence of hypocapnia on the first arterial blood gas after initiation of mechanical ventilation (Cheema et al. 2007). The mean PaCO_2 was lower with A/C alone ($p=0.02$), and the incidence of hypocapnia trended higher 57 % vs. 32 % compared to A/C+VG ($p=0.11$). They noted a significant negative correlation between gestational age and PaCO_2 . The fact that the smallest infants had PaCO_2 values above target range reflects the impact of fixed instrumental dead space that was documented. When infants <25 weeks were excluded, the decrease in out of range PaCO_2 values became significant. The study limitations underscore the importance of selecting appropriate V_T targets.

More recently, Lista et al. studied 40 infants with RDS randomly assigned to A/C+VG ($V_T=5$ mL/kg) or HFOV using the Babylog 8000 plus (Lista et al. 2008). IL 6, IL8, and TNF were measured in tracheal aspirate on days 1, 3, and 7. In contrast to the similar study by Dani et al. (2006), the duration of requirement for supplemental oxygen was shorter, and the IL 6 levels were lower with A/C+VG, possibly because Lista used a more appropriate PEEP of 5 cmH₂O

and the T_i was likely longer with the A/C than the PSV used by Dani. The absence of dramatic differences in lung volume strategy favoring HFOV perhaps allowed for a more unbiased evaluation of the effect of VG.

To address the effect of the instrumental dead space (IDS) of the flow sensor and to establish normative data for target V_T in the smallest infants, Nassabeh-Montazami et al. reviewed 344 paired observations of V_T and normocapnic arterial blood gas measurements in 38 infants <800 g at birth (mean 627 g, range 400–790 g) during the first 24 h of life (Nassabeh-Montazami et al. 2009). The V_T /kg required for normocapnia was inversely related to birth weight (BW) ($r = -0.70$, $p < 0.01$) indicating an effect of the fixed IDS. Mean V_T for infants 500 g was 5.9 mL/kg vs. 4.7 mL/kg for those 700 g ($p < 0.001$). Interestingly, the absolute mean set and measured V_T was 3.11 and 3.17 mL, respectively, barely above the estimated instrumental plus anatomic dead space of 3.01 mL. With normal PaCO_2 values, 47 % of all V_T values were at or below dead space volume. The key conclusions were that the impact of IDS is limited even in the tiniest infants but must be taken into account when choosing VG settings. Effective alveolar ventilation apparently occurs with V_T at or below dead space, suggesting that a spike of fresh gas penetrates through the dead space gas, similar to what occurs with high-frequency ventilation. Keszler et al. subsequently confirmed this phenomenon in a bench study where using conventional rates they clearly demonstrated the ability to remove CO_2 with V_T below measured dead space (Keszler et al. 2012). In a companion study, Keszler et al. showed that with advancing postnatal age, the V_T needed to maintain adequate ventilation rose from a mean of just over 5 mL/kg on day 1 to over 6 mL/kg by the end of the 3rd week despite mild permissive hypercapnia (mean PaCO_2 of 53) in infants <800 g (Keszler et al. 2009).

More recent studies focused on determining appropriate V_T in infants with a variety of underlying pulmonary disorders in order to guide the clinician in choosing a correct V_T . Infants with meconium aspiration syndrome (MAS) required larger V_T than those with more homogeneous

lung disease, as might be expected because of the increased alveolar dead space in the infants with air trapping in the infants with MAS (Keszler 2006). Furthermore, contrary to popular belief, infants with congenital diaphragmatic hernia needed similar V_T to those without lung hypoplasia (Sharma et al. 2010). This should not be surprising when one considers the fact that their CO_2 production is not different from other infants of similar size and therefore they need the same V_E .

In summary, the body of literature in neonates concerning the use of dual control modes such as volume-targeted ventilation continues to expand, but none of the individual studies are sufficiently large enough to clearly demonstrate the benefit of this approach in terms of major long-term outcomes. Although volume guarantee has been studied most extensively, it remains to be seen whether there are important differences between different modes of volume-targeted ventilation and if these results can be extrapolated to other modalities of volume-targeted ventilation.

21.5.1.3 Clinical Experience in Pediatric Patients

A dual control mode such as PRVC (Maquet Servo-i and GE) is a commonly utilized mode in the PICU for pediatric patients. The advantages of this mode, which include the ability to minimize the PIP with a guaranteed V_T with a decelerating flow waveform for improved gas distribution, are ideal features to maintain a protective lung strategy. The limitations of this mode are the issues created during spontaneous breathing (Branson and MacIntyre 1996). These include a potential to cause or worsen auto-PEEP, potential for decreased support with increased patient demand, and concerns over the need for increased sedation to decrease demand. These disadvantages can be limited by combining PRVC with another mode such as volume support when the patient begins to trigger spontaneously. Since PRVC is time cycled, transitioning the patient to flow-cycled mode such as volume support may improve synchrony. In small infants, the transition from PRVC to volume support may be problematic because of potential for episodes of apnea and reduced respiratory drive. It is common in

the ICU when transitioning a patient from PRVC to volume support to initially utilize a transition mode such as auto-modeTM to reduce the incidence of alarms and apnea (Holt et al. 2001).

21.5.2 Volume Assured Pressure Support

Volume assured pressure support (VAPS) and pressure augmentation are described as a dual control within a breath mode where the ventilator switches from pressure control to volume control within the breath. In this mode, the clinician chooses a volume target and the breath begins as a pressure-limited, flow-cycled breath, either spontaneously (pressure support) or mechanically. When inspiratory flow has decelerated to the minimum set level, delivered volume is measured. If the target volume has been met or exceeded, the breath ends. If the delivered volume has not met the volume assurance target, the breath is transitioned to a volume-targeted breath by prolonging inspiration at the minimum flow and increasing the inspiratory pressure until the delivered volume has been obtained. The theoretical advantages of these modes are the ability to maintain constant V_T and minute volume with a resultant lower work of breathing. Again, little evidence is available on its use in infants and children and there have been no recent studies demonstrating its use.

21.6 Pressure Support Ventilation

During PSV every spontaneous inspiration triggers a flow-cycled ventilator breath. In this way, the duration of the mechanical inspiratory phase is determined by the end of the spontaneous inspiratory effort or the point near the end of lung inflation. Most ventilators terminate inspiration when the inspiratory flow decays below a fixed fraction of its highest value, whereas other devices allow the operator to set the threshold fraction.

PSV can be provided as a stand-alone mode where an IMV rate provides backup ventilation during periods of apnea or in combination with

SIMV (that becomes IMV in apnea) where spontaneous breaths between SIMV breaths are assisted by PSV. In both modes, the PSV level differs from the peak pressure of the SIMV or IMV breaths.

The objective of PSV is to provide a degree of inspiratory unloading where the set pressure support level alleviates the effort required to overcome the resistance of the endotracheal tube and elastic or resistive loads imposed by the underlying lung disease on the respiratory pump. For instance, an infant with a respiratory compliance of 0.5 mL/cmH₂O that requires a 5 mL V_T and receives pressure support of 5 cmH₂O would need to generate roughly 5 cmH₂O to produce 10 cmH₂O of transpulmonary pressure to achieve such V_T . In that way, the infant would perceive a higher compliance since 5 cmH₂O generated by the diaphragm achieve the 5 mL V_T , i.e., PSV is providing some degree of mechanical unloading. How much unloading is provided by a given pressure support level varies between infants and depends on the mechanical characteristics of the respiratory system.

In many instances, PSV results in a reduction in spontaneous breathing effort with relatively unchanged V_T , while the duration of the positive pressure cycle is determined predominantly by the duration of the spontaneous inspiratory effort. On the other hand, PSV levels that exceed what is required to overcome the respiratory loads almost invariably result in a greater V_T with the duration of the supported breath determined by the time constant of the respiratory system. The latter however, is not concordant with the manner in which PSV was conceived as providing only the support necessary to overcome the excessive work of breathing.

During PSV, there is three distinct phases: (1) recognition of the beginning of inspiration, (2) pressurization, and (3) recognition of the end of inspiration.

21.6.1 Initiation of the Cycle

Triggering or initiation of the respiratory cycle during PSV is patient initiated, and the sensitivity of this initiation is adjustable by the clinician.

Trigger sensitivity may be adjusted to improve a patient's ability to initiate a breath. There is a delay that occurs between when the patient initiates a breath and the start of pressurization of the breath. This delay is termed trigger delay. Most ventilators respond in less than 100 ms, but there is some variability among ventilator models (Thille et al. 2009). The rate of pressurization also varies among ventilator models, but many allow for clinician adjustment. A regulatory mechanism should ensure the appropriate flow reaches the set pressure support level and keeps the pressure constant until expiration occurs. A high speed of pressurization will produce a square pressure wave, whereas a lower speed of pressurization will attenuate this square shape.

21.6.2 Cycling Off to Expiration

Cycling off usually occurs when inspiratory flow falls below a specific threshold. This threshold can be changed on many ventilators. Sensing a small change in pressure above the set pressure support level, which may represent patient expiratory effort, may be used alone or in combination with the flow threshold for cycling off. There is also typically a time limit set for the duration of inspiration. The presence of a time limit offers a safety mechanism when a leak is present in the circuit, thus incapacitating flow cycling.

21.6.3 Expected Physiologic Effects

The expected physiologic effects are diverse. These are discussed in further detail in a previous chapter. Briefly, these effects include effects on breathing pattern since during PSV the patient keeps control of the respiratory rate, V_T , and inspiratory duration. Since the patient has control over all aspects of the breath, PSV has been termed "physiologic." However, today this control of a patient's breath is no longer unique to pressure support as other modes offer the same patient controls during spontaneous breathing. The degree of expected physiologic effect is proportional to the level of pressure given. It has

been demonstrated in adult patients that a high level of work of breathing during the weaning period leads to a substantial increase in oxygen demand the oxygen cost of breathing. It is important to note that the level of support is clinician determined, thus the level of support might be insufficient or excessive in circumstances where the patient's respiratory compliance or respiratory resistance varies significantly.

Other expected physiologic effects from offering adequately assist to respiratory muscle activity include improved efficiency of the patient's effort and reduced patient's work load to an acceptable level. The ability to measure work of breathing in infants and children can be difficult, and thus, actually measuring the advantages of any ventilator mode is problematic. However, there is adequate animal and adult data to support the conclusion that PSV is efficient in decreasing the work performed by the patient. This reduction in work is important in pediatric patients for a number of physiologic reasons described above. The level of extra work is partially related to the imposed work of the patient's endotracheal tube and triggering aspects of the ventilator. This imposed work can be exaggerated in neonatal and pediatric patients secondary to the size of their endotracheal tube and the work necessary to overcome the triggering aspects of the ventilator. However, resistance of the endotracheal tube are minimal in endotracheal tubes larger than 3.5 I.D. (Manczur et al. 2000b). The question that is still unanswered in neonatal and pediatric patients is whether these breaths are better controlled by the clinician determining the level of pressure, as in PSV, or by a clinician determined V_T as available in a dual control mode such as volume support ventilation.

21.6.4 Clinical Use of Pressure Support in Neonates

In neonates PSV can be used very much in the same manner as A/C during both the acute and weaning phase of respiratory failure, but it is predominantly used during the weaning phase and often in infants patients with more chronic

ventilator need. In PSV, every spontaneous breath is assisted, and mechanical inspiratory phase is terminated at the end of the spontaneous inspiration or end of inflation. It is generally believed that in this manner, the infants have a greater control of his/her ventilation. However, a consistent respiratory drive is required for use of PSV as stand-alone strategy. When this is not the case, a backup IMV rate maintains ventilation when apnea occurs, and by providing larger V_T 's this preserves lung volume and avoids lung collapse.

PSV is primarily aimed at providing a boost to the spontaneous inspiratory effort by applying positive pressure breaths with peak pressures just sufficient to compensate for excessive mechanical loads. When PSV is used as an adjunct to SIMV as shown in Fig. 21.3, it provides support to the otherwise unassisted spontaneous breaths to avoid respiratory fatigue or hypoventilation and reduce the need for high SIMV rates. Nonetheless, an SIMV rate with higher positive pressure cycles is still required since it provides a continuous background ventilation level and assures adequate ventilation during periods of apnea. Compared to SIMV alone, the use of PSV in this manner reduced breathing effort by providing support at pressure levels that were half of pressures of the SIMV cycles; whereas higher PSV levels increase the V_T of the supported breaths leading to an increase in V_E and a reduction in breathing frequency (Osorio et al. 2005; Patel et al. 2009; Gupta et al. 2009). In a randomized controlled trial, Reyes et al. showed that PSV as an adjunct to SIMV facilitated weaning in comparison to SIMV alone in preterm infants of BW <1,000 g (Reyes et al. 2006). In that study, PSV levels ranging between 30 and 50 % of the peak pressure of the SIMV cycles were sufficient to maintain acceptable PaCO_2 levels with lower SIMV rates. The beneficial effects of the faster weaning with PSV were more striking among infants of BW >700 g rather than in the smaller infants. This was likely due to a more mature respiratory drive required for consistent triggering of PSV.

PSV has the advantage that every breath is flow cycled, therefore avoiding the issue of prolonged pressure plateau. On the other hand, and similarly to A/C, gas leaks around the endotracheal tube can produce autocycling up to high

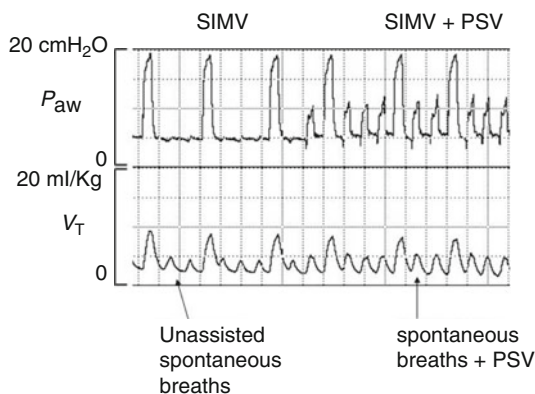


Fig. 21.3 Recordings of airway pressure (P_{AW}) and tidal volume (V_T) during SIMV alone and during SIMV with PSV as an adjunct. V_T from spontaneous breaths assisted by PSV is larger from unassisted spontaneous breaths during SIMV. This is achieved with PSV levels that are a fraction of the peak pressures the SIMV cycles

ventilator rates. This can produce gas trapping and hyperventilation. In PSV, because the breath is terminated when inspiratory flow decays towards baseline, gas leaks during the inspiratory phase may cause the inspiratory flow to stay above the termination threshold prolonging the duration of the cycle. In most ventilators, the termination threshold can be adjusted and a maximal inspiratory duration must be set to assure safety.

21.6.4.1 Clinical Use of Pressure Support in Pediatric Patients

In pediatric PSV can be used very much in the same manner as A/C during both the acute and weaning phase of respiratory failure, it is predominantly used during the weaning phase. In PSV, every spontaneous breath is assisted and mechanical inspiratory phase is terminated at the end of the spontaneous inspiration or end of inflation. In this way, the patient has a greater control of his/her ventilation. A backup IMV rate maintains ventilation when apnea occurs and by providing larger V_T 's preserves lung volume and avoids lung collapse. In pediatric patients, this strategy may be more efficient by ensuring adequate levels of PEEP to maintain lung volumes and maintaining the size of the supported breath similar to what is offered during the pressure support breath. It is important to note that failure of a patient to tolerate conversion to a support mode

is not a failure of the mode, but a signal that the patient is not ready for this conversion.

In pediatric patients there are no exact guidelines for the clinical use of PSV (Vignaux et al. 2013). Adding PSV augments the pressure differences between the alveoli and the ventilator circuit, resulting in higher V_T 's and inspiratory flow rates than spontaneous breathing alone. Often, the PSV is adjusted to achieve a V_T of 6–8 mL/kg. Assessment of accessory muscle activity and respiratory rate may assist in determining the ideal level of PSV (Brochard et al. 1989). Targeting a respiratory rate less than 32 bpm may be associated with decreased work of breathing (Yanez et al. 2008); however, a lower target rate (<25 bpm) may prolong weaning duration.

PSV is commonly used during weaning and assessment of extubation readiness, although evidence remains mixed. A low level of PSV can be used to simulate spontaneous breathing trials. PSV can also be used in combination with SIMV as a means for weaning, but there is not much data to support this. Using a low level of PSV has been shown to be equivalent or superior to T-piece trials in adults and infants (Esteban et al. 1997; Farias et al. 2001; Matic and Majeric-Kogler 2004).

21.6.4.2 Advantages and Limitations of Pressure Support in Pediatric Patients

Pressure support ventilation has many reported benefits. Since it is a patient-triggered, pressure-limited mode of positive pressure during the inspiratory phase, commonly, a pressure plateau is maintained until the patient's inspiratory flow decreases to a specified level at which time exhalation occurs. In this mode, the patient determines the initiation of the inspiration, T_I , flow, and V_T and the termination of the inspiratory phase. A potential limitation is that the patient's effort, dependent on the preset pressure limit and respiratory system impedance, determines the V_T . Subsequently, T_I and V_T can vary significantly between breaths.

Patient inspiratory effort to trigger the ventilator comprises 10–30 % of total breathing effort. Trigger delay directly correlates with respiratory drive (the more time in the trigger phase, the more respiratory effort required to trigger the

ventilator). The pre-trigger/trigger phase of the breath consists of a patient effort or trigger delay (the time between the start of patient effort and the beginning of ventilator pressurization) and the response time of the ventilator (time between the beginning of ventilator pressurization and the return of pressure to baseline). Even though PSV is commonly thought to reduce patient effort, this is only true if the rise in flow is commensurate with the patient's demand. In this scenario, where it does match patient demand, there may be too rapid a rise in flow or flow may be inadequate to meet the patient's effort (MacIntyre et al. 1997). In either case, patient-ventilator asynchrony can result. This is not unique to PSV, but can be exaggerated in pediatric and neonatal patients in spontaneous breathing modes due to the patient's anatomy and physiology. It is important to note that patient effort is actually greater when the patient does not meet ventilator trigger threshold than when trigger threshold is reached (Tobin 2001). Since the most important physiologic aspect of PSV is its ability to better match the patient's inspiratory flow demands, thereby minimizing respiratory muscle effort as compared to other modes of mechanical ventilation, these advantages are lost if asynchrony occurs.

21.7 PSV During Noninvasive Ventilation

Noninvasive ventilation (NIV) delivers gas through a face or nasal mask, providing ventilatory support without endotracheal intubation (Yanez et al. 2008). Noninvasive ventilation is beneficial as an alternative to endotracheal intubation for adults with neuromuscular disorders, chronic obstructive pulmonary disease, respiratory distress, and cardiogenic pulmonary edema (Demoule et al. 2006; Antonelli et al. 1998; Minuto et al. 2003). Pressure support ventilation is the usual mode of ventilation utilized with NIV. There is less data available for the use of NIV in children, but the initial studies are promising. In a retrospective series of 114 children with varying disease processes requiring NIV with PSV, Essouri et al. found a 77 % success rate

in improving respiratory distress and avoiding endotracheal intubation (Essouri et al. 2006). Similarly, in a randomized, prospective study, Yanez et al. demonstrated improved oxygenation and respiratory effort in children with acute hypoxemic respiratory failure (Yanez et al. 2008). They also had a 47 % reduction in the rate of intubation (Yanez et al. 2008). The use of PSV during NIV does have limitations especially when there is evidence of a considerable leak with the mask interface causing asynchrony. This is discussed in detail in a subsequent chapter.

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Part VII

Clinical Use of Nonconventional Modes of Ventilator Support

22.1 High-Frequency Oscillatory Ventilation (HFOV)

22.1.1 HFOV in Neonates

Sherry E. Courtney and David J. Durand

Educational Aims

- To be aware of the history of HFOV, both animal studies and clinical trials
- To understand the major components of HFOV physiology
- To describe clinical situations in which HFOV may be useful
- To understand the basic ventilator management required during HFOV use

22.1.1.1 Introduction

High-frequency oscillatory ventilation (HFOV) is now a mainstay of respiratory care for the neonatal patient. In this chapter, we will define HFOV as those ventilators with a “true” active expiratory phase created by a piston or diaphragm. Jet ventilation and flow interrupters are discussed elsewhere in this book.

22.1.1.2 History of HFOV: The Animal Studies

In 1915, Henderson et al. observed that panting dogs were able to maintain adequate alveolar ventilation while breathing at high frequencies.

They postulated that maintenance of normal ventilation with tidal volumes of less than the anatomic dead space might be occurring (Henderson et al. 1915). These findings were confirmed by Briscoe et al. in 1954 in the first description of high-frequency ventilation (Briscoe et al. 1954). Through the 1970s, a series of investigations demonstrated that HFOV could effectively support gas exchange (Jonzon et al. 1971, 1973; Sjostrand 1977; Sjostrand and Eriksson 1980).

In the 1980s, intense animal and human research on HFOV confirmed it as a viable technique for ventilation. The work of deLemos and colleagues using the infant baboon model set the stage for human trials and found that HFOV, when compared to the conventional ventilation used at that time, resulted in less lung injury (deLemos et al. 1987, 1989; Meredith et al. 1989; Kinsella et al. 1991). By the early 1990’s, there was a wealth of information from multiple investigators, using multiple animal models, suggesting that HFOV caused less injury to the immature lung than did “conventional ventilation” (Hamilton et al. 1983; Truog et al. 1984; McCulloch et al. 1988; Jackson et al. 1994). The generally accepted mechanism of this superiority was the ability to support gas exchange with small tidal volumes and high mean airway pressure, thereby minimizing injury from both overdistention and atelectasis.

22.1.1.3 History of HFOV: The Clinical Trials

Though the superiority of HFOV over conventional ventilation (CV) has not been proven in the

human neonate with respiratory distress syndrome (RDS), its equivalence has been clearly demonstrated when compared to modern techniques of CV that focus on minimizing barotrauma and volutrauma.

The HiFi study of 1989 was the first large multicenter trial of HFOV compared to CV. At that time investigators and clinicians were still learning how to best apply this new technology. Though the HiFi trial showed no benefit of HFOV and possible increases in intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL), the use of an optimal mean airway pressure to open the lung was not applied in that study (HiFi Study Group 1989).

Multiple smaller studies of HFOV vs. CV followed the HiFi trial, some of which showed benefit of HFOV and some, equivalence. No study showed increased lung damage in patients receiving HFOV. Clinical trials on infants showed that HFOV could be safe and effective (Clark et al. 1992; HiFO Study Group. 1993; Ogawa et al. 1993; Gerstmann et al. 1996), and an oscillator was approved in the United States for clinical use in neonates in 1991, the SensorMedics 3100.

Two large randomized trials were published in 2002. Courtney et al. found, in 500 very low birth weight infants, a reduction in bronchopulmonary dysplasia (BPD) and time on ventilator support when infants who required surfactant were treated with HFOV within 6 h of birth and were extubated directly to nasal continuous positive airway pressure (nCPAP) (Courtney et al. 2002). Johnson et al. found no difference in BPD in over 800 infants randomized at birth and treated with HFOV for a minimum of 5 days (Johnson et al. 2002).

A Cochrane meta-analysis of the HFOV trials found no evidence for benefit or harm when HFOV was compared to CV in infants with RDS (Cools et al. 2009). A recent individual patient data meta-analysis confirmed these results (Cools et al. 2010). The predominant potential benefit assessed in these trials was reduction in death and/or chronic lung disease; the predominant adverse effects assessed were severe IVH and PVL.

An important caveat in interpreting these clinical trials and the meta-analyses is that the trials were conducted in an era when ventilator man-

agement of very low birth weight infants was different than current approaches. Many of the babies included in these studies would probably not be ventilated at all or would be extubated much earlier in the current era. In addition, our current understanding of the multifactorial nature of chronic lung disease makes the results of these studies less surprising (Baraldi and Filippone 2008). It is also reassuring that early concerns of possible increased neurological damage with HFOV have not been borne out.

22.1.1.4 Physiology of HFOV

Chang, in his classic article of 1984, described the mechanisms of gas transport during HFOV (Chang 1984). The physics of gas exchange with HFOV are complex and dealt with more fully elsewhere in this text. In brief, HFOV can be broadly described as enhanced mixing between gas in the upper airway and gas in the alveoli. While the mean airway pressure holds the lung open and promotes oxygenation, the oscillations essentially “shake” the gas, promoting rapid and efficient gas exchange. As HFOV amplitude is increased, there is increased shaking, which results in increased mixing and increased gas exchange.

An essential part of HFOV physiology is the role the upper airway plays as a low-pass filter between the upper airway and the alveoli, where high frequencies are attenuated or dampened more than low frequencies. For example, at 1 Hz (60 breaths/min), essentially all of the pressure seen in the upper airway with each ventilator inflation is transmitted to the alveoli. However, at 10 Hz (600 breaths/min), there is significant attenuation of the amplitude signal by the airways. At 20 Hz, the attenuation is even more pronounced, causing even less of the amplitude pressure to be transmitted to the airway. Thus, changes in HFOV frequency have profound effects on the amount of pressure transmitted to the alveoli and on the efficacy of gas mixing.

22.1.1.5 When to Consider HFOV

22.1.1.5.1 General Considerations

HFOV should be considered early in the course of respiratory failure, prior to lung damage from

volutrauma and/or barotrauma. Clearly when CV cannot be employed safely – when high volumes and pressures must be used to effect gas exchange – HFOV and other forms of high-frequency ventilation can be lifesaving.

“Rescue” of the lungs following attempts to sustain oxygenation and ventilation with high tidal volumes or high pressures is seldom successful or at best may salvage an infant who already has sustained significant lung damage. Infants on CV with sufficient positive end expiratory pressure (PEEP) and who require tidal volumes of more than 6 ml/kg or peak inspiratory pressures of greater than 25 cm H₂O should be considered for some form of high-frequency ventilation. HFOV may be very effective for the following conditions.

22.1.1.5.2 Respiratory Distress Syndrome

RDS can be treated extremely effectively with HFOV. First-intention use, upon arrival of the infant to the NICU, is preferred by some centers (Rimensberger et al. 2000; De Jaegere et al. 2006). Others use HFOV for infants who do not wean quickly from CV after surfactant is given or whose condition worsens. Requirement of dangerously high tidal volumes or peak inspiratory pressures necessitates intervention, usually with HFOV. Surfactant can be given during HFOV without disconnecting the ventilator by using an in-line catheter.

22.1.1.5.3 Persistent Pulmonary Hypertension (PPHN) and Meconium Aspiration Syndrome (MAS)

Though PPHN and MAS are not always coexistent, they often occur together. HFOV is the treatment of choice for PPHN with lung disease requiring use of inhaled nitric oxide (iNO). Kinsella et al. found that significantly more infants responded to HFOV plus iNO than with iNO and CV or with HFOV alone (Kinsella et al. 1997).

22.1.1.5.4 Abdominal Surgery/NEC

Infants who require abdominal surgery, such as with omphalocele or gastroschisis, or infants who

develop NEC may require high ventilator settings due to abdominal distention. These infants may also have concurrent lung disease. Use of HFOV in these situations can support the infant during the recovery period.

22.1.1.5.5 Hypoplastic Lungs

Infants with hypoplastic lungs from a variety of causes such as Potter’s sequence or certain skeletal anomalies may require ventilator support for long periods of time. Use of CV in these babies may require unsafe parameters and may often lead to air leak. HFOV can provide long-term support for potentially viable infants with lung hypoplasia.

22.1.1.5.6 Surgery

Nearly any surgical procedure can be performed while an infant is on HFOV. A pediatric anesthesiologist or neonatologist skilled in its management should be at the bedside. Periodic assessment of blood gases or use of both continuous saturation and transcutaneous CO₂ monitoring should be done. Patent ductus arteriosus (PDA) ligation on HFOV is done at the bedside during HFOV in many NICU’s. Stability of the lung inflation during lung retraction in PDA ligation is often better than with CV, and the infant may therefore better tolerate the surgery. Other surgical procedures, such as laparotomy for NEC, are also often performed during HFOV.

22.1.1.5.7 Congenital Diaphragmatic Hernia (CDH) and Other Conditions

HFOV is often needed during treatment of CDH to prevent the need for high peak pressures during CV and to prevent air leak. Many other, more rare, congenital anomalies may also respond to use of HFOV. Hydrops fetalis, chylothorax, and cystic adenomatoid malformation are some examples.

22.1.1.5.8 Extracorporeal Membrane Oxygenation (ECMO)

Infants on ECMO can be managed on HFOV. Care must be taken to assure that the vibrations

of the oscillator do not dislodge the ECMO cannulas.

22.1.1.6 Management of the Infant on HFOV

The lung, especially when becoming diseased or recuperating from disease, is a dynamic organ with changes in its mechanical properties that will depend on the disease process, the stage of that process, and the interventions we impose. We must be diligent about not only how and when we increase ventilator settings but how and when we wean them so that we do not create iatrogenic complications and lung damage.

22.1.1.6.1 Mean Airway Pressure (MAP)

As with any form of ventilation, it is critically important to recruit the lung. Lung recruitment during HFOV is best done by increasing the mean airway pressure (MAP) until the FiO_2 is at a minimum. At that point, the MAP can be slowly decreased until the FiO_2 starts to rise. The MAP is then set at the point just before this rise in FiO_2 occurred. The infant is thus ventilated on the descending limb of the pressure-volume curve (Tingay et al. 2006).

22.1.1.6.2 Frequency and Amplitude

In HFOV, frequency is typically measured in Hertz (Hz), where 1 Hz = 1 cycle/s or 60 cycles/min. Optimal frequency depends on the size of the patient and the underlying lung disease. Most oscillators function between 3 and 20 Hz. However, in the neonate, 8–12 Hz appears to be the most effective. Higher frequency may result in air trapping due to the shortened expiratory time. Lower frequency results in large increases in tidal volume. For most preterm infants with restrictive lung disease such as RDS, we recommend 10–12 Hz. Term infants with obstructive disease such as meconium aspiration syndrome may require 8 Hz.

Amplitude should be that which maintains the PCO_2 at the desired level. We recommend transcutaneous CO_2 monitoring for infants on HFOV. Oscillators are powerful ventilators and PCO_2 can be easily driven to dangerously low

levels very quickly. Low PCO_2 in the preterm infant has been associated with PVL (Shankaran et al. 2006).

22.1.1.6.3 Inspiratory Time

The recommendations of the manufacturer should be followed. Some oscillators, such as the Humming series, have a fixed inspiratory time (IT) of 50 % of the respiratory cycle. Others, such as the Babylog 8000, vary with the frequency. Others, such as the SensorMedics 3100A, may be operator-set; however, the manufacturer recommends a 33 % IT, due to lack of data as to the effects of a longer percent inspiratory phase.

22.1.1.6.4 Flow

Increased flow can cause increased turbulence in the airways and, therefore, increased resistance. The lowest flow at which the MAP is maintained is appropriate.

22.1.1.6.5 Weaning

As previously mentioned, timely and appropriate weaning is crucial to prevent complications and lung damage. Particularly following surfactant administration, the compliance of the lung may improve rapidly, necessitating rapid weaning as well. With proper lung recruitment, the FiO_2 required by most infants will be low, nearly always below 0.40 and often below 0.30. Once the infant is stable at this point with acceptable blood gases and a chest radiograph that shows good lung recruitment, MAP can be weaned. Rate of wean will depend upon the underlying lung disease. An infant with RDS who has responded to surfactant can often be weaned from HFOV within hours.

Changes in MAP require the lung to recruit or derecruit, a process that takes a little time, depending on the degree of parenchymal disease. MAP changes should usually be made no more frequently than every 30–60 min to allow for stabilization of the lung at the new MAP. Any evidence of overdistention, such as flat diaphragms or small heart on chest radiograph, should be accompanied by aggressive weaning of MAP. Amplitude can be weaned as needed to keep the PCO_2 in an acceptable range.

22.1.1.6.6 Care of the Infant on HFOV

Infants on HFOV do not require increased sedation. They are usually quite comfortable and may even become apneic. Unlabored breathing is perfectly normal during HFOV; labored breathing should alert the caregiver to the possible need for increased ventilator support. Sedation and pain relief should be used as needed for procedures and discomfort.

We recommend in-line suctioning for infants on HFOV to maintain the lung volume and assure accurate positioning of the suction catheter tip, as well as for infection control.

Infants on HFOV can be positioned prone or supine. They can be nursed under a radiant warmer or in an incubator. They can be held by the parents. Infants should be repositioned at least every 12 h to prevent pressure sores. Repositioning the infant can be done without disconnecting the ventilator.

22.1.1.6.7 Extubation

Infants can be extubated directly from HFOV to nCPAP. In general, amplitude should be weaned so that the infant is breathing spontaneously above the ventilator prior to extubation. Extubation parameters include MAP of 6–8 cm H₂O, relatively clear chest radiograph, and FiO₂ of 0.30 or less in most cases. Small babies will benefit from a caffeine load prior to extubation. Some infants may be successfully extubated from HFOV at even higher levels of MAP and FiO₂.

Conclusion

HFOV has increased our options for the care of many newborn infants with significant respiratory problems. After more than three decades of research and clinical use, it is clear that (1) HFOV is an effective technique for gas exchange; (2) HFOV is at least as safe as conventional ventilation; and (3) if there are advantages to HFOV over conventional ventilation, it is for cases where it is used to prevent lung injury caused by overdistention and/or atelectasis, particularly in severe restrictive disease. It must be used properly, as with any mechanical ventilator, to assure the best response and to avoid preventable complications.

Essentials to Remember

- HFOV is at least equivalent to conventional ventilation in infants with RDS and may provide significant advantages in some circumstances and other disease states.
- HFOV is not associated with adverse effects either in the lung or in the brain.
- As with any form of ventilation, it is critically important to appropriately recruit the lung during HFOV.
- Infants may be successfully extubated directly from HFOV to nCPAP.

22.1.2 Pediatric HFOV

Gerhard K. Wolf and John H. Arnold

Educational Aims

- Reviewing the evidence-based use of HFOV in pediatric hypoxemic respiratory failure
- Assessing the patients that are considered for a trial of HFOV
- Initiation of HFOV in pediatric patients
- Reviewing the patient population that may not benefit from HFOV

22.1.2.1 Evidence for High-Frequency Ventilation in Pediatric Patients

High-frequency oscillatory ventilation (HFOV) has been compared to conventional ventilation in neonatal (Courtney et al. 2002, Johnson et al. 2002), pediatric (Arnold et al. 1994), and adult (Derdak et al. 2002) trials. Although none of the studies showed an improvement in mortality or ventilator-free days during HFOV, there is a large body of evidence that HFOV is a safe strategy of ventilation allowing rapid and effective recruitment of lung volume, without significantly increased adverse events during HFOV as compared to conventional ventilation.

Data from a neonatal trial (Courtney et al. 2002) indicated a small benefit of HFOV in terms of pulmonary outcome for very low birth weight infants. A trial in pediatric patients (Arnold et al. 1994) showed a significant improvement in oxygenation during HFOV compared with a conventional ventilatory strategy and a decreased need for supplemental oxygen at 30 days. Aggressive recruitment of lung volume during HFOV is often achieved using higher mean airway pressures compared to conventional ventilation. A multicenter experience from different pediatric intensive care units in the United States demonstrated significant increases in mean airway pressure and concomitant increases in oxygenation index when patients were transitioned from conventional ventilation to HFOV (Arnold et al. 2000). HFOV has been advocated as a rescue strategy in patients who are failing conventional ventilation, but smaller single-center studies in children (Fedora et al. 2000; Ben Jaballah et al. 2005) and adults (Mehta et al. 2001) also suggested some benefit towards an early implementation of HFOV. However, an early use of HFOV often implies administering neuromuscular blocking agents to a patient early in the course of disease, which may have to be weighed carefully against potential side effects of prolonged neuromuscular blockade.

Utilizing HFOV as a recruitment strategy may result in increased delivery of inhaled gases such as inhaled nitric oxide (iNO) to recruited lung areas. Utilizing data from a randomized, controlled multicenter trial of the use of iNO in pediatric acute hypoxemic respiratory failure, one study indicated that the use of HFOV plus iNO resulted in a greater improvement in oxygenation compared to a strategy combining conventional ventilation and iNO (Dobyns et al. 2002).

A randomized multicenter trial comparing HFOV to conventional ventilation in adult patients with acute respiratory distress syndrome (Derdak et al. 2002) resulted in an improvement in early oxygenation during HFOV using an aggressive lung recruitment strategy; however, this effect was lost after

24 h. The early positive oxygenation response during HFOV may be explained by the prevalence of higher mean airway pressures during HFOV as compared to conventional ventilation. There were no significant differences in mortality or ventilator-free days between the groups. The use of HFOV in this study was not associated with increased adverse hemodynamic effects, evidence of barotrauma, or mucous plugging when compared to conventional ventilation.

22.1.2.2 Ventilators Used for High-Frequency Ventilation in the Pediatric Population

There are a variety of high-frequency devices available. Most devices are reserved for neonatal patients and small infants. The SensorMedics 3100 A/B (Viasys, Yorba Linda, CA) is the only device that generates effective gas exchange in neonates, children, and adults. Two devices are available. The SensorMedics 3100 A is being used for neonates and children, and the SensorMedics 3100 B is approved for adults and larger children over 35 kg. For the 3100 A, the bias flow ranges from 0 to 40 l/min, mean airway pressures range from 3 to 45 cm H₂O, and the frequency ranges from 3 to 15 Hz (180–900 breaths/min). In comparison to the 3100 A, the 3100 B has a more powerful diaphragm, can provide a larger bias flow (0–60 l/min), and can apply higher mean airway pressures of up to 55 cm H₂O.

22.1.2.3 Initiating HFOV in Pediatric Respiratory Failure

22.1.2.3.1 Indication and General Considerations

HFOV is considered when conventional modes of ventilation fail to provide adequate oxygenation or adequate alveolar ventilation in pediatric patients with acute respiratory distress syndrome (ARDS). Failing conventional ventilation can be indicated by arterial hypoxemia despite a $\text{FiO}_2 \geq 0.7$ and a mean airway pressure exceeding 15 cm H₂O. Recent pediatric multicenter trials involving ventilation algorithms have used the oxygenation index (OI) ($\text{FiO}_2 \cdot \text{mean airway}$

pressure • 100/PaO₂) to determine the transition from conventional ventilation to HFOV; the transition to HFOV was considered when the OI was 15 and rising and the use of HFOV was mandated with an OI of 20 (Curley et al. 2005; Fineman et al. 2006).

Patients transitioning to HFOV should have an arterial line for invasive blood pressure and arterial blood gas monitoring and central venous access for monitoring of the central venous pressure. While neonates can breathe spontaneously during HFOV, the bias flow of the system is not sufficiently high to support spontaneous ventilation in pediatric patients (van Heerde et al. 2006). This effect was demonstrated in a study using an artificial lung device during HFOV. The work of breathing was considerably increased when an (simulated) adult or larger pediatric patient was breathing spontaneously during HFOV. During the simulation of a newborn breathing spontaneously, the work of breathing was markedly reduced (van Heerde et al. 2006). Outside the neonatal population, neuromuscular paralysis is required in patients to prevent depressurization of the circuit resulting in alveolar derecruitment (Heulitt et al. 2008; Wolf and Arnold 2007).

22.1.2.3.2 Considerations for Exclusion

22.1.2.3.2.1 Obstructive Airway Disease

Diseases with increased airway resistance as seen in status asthmaticus, bronchiolitis, and reactive airway disease are generally associated with hypercarbia and air trapping rather than arterial hypoxemia. The application of an aggressive recruitment strategy may increase the incidence of air trapping and the risk of extrapulmonary leak. However, infants with respiratory syncytial virus (RSV) infections may present with both acute hypoxemic respiratory failure due to acute lung injury and impaired CO₂ elimination secondary to small airway obstruction. The successful use of HFOV in infants with RSV infection has been reported in a few cases, leading to reversal of hypoxemia and recruitment of atelectasis while achieving adequate CO₂ removal (Berner et al. 2008). The use of HFOV in intubated children with status asthmaticus to

facilitate CO₂ removal has also been reported (Duval and van Vught 2000). However, utilizing HFOV to achieve adequate CO₂ removal in this setting often requires the combination of a high amplitude and a low device frequency, resulting in increased delivered tidal volumes during HFOV. Since delivered tidal volumes are not measured during HFOV and may be as high as 5 ml/kg during clinical use (Sturtz et al. 2008), a high-amplitude low-frequency strategy may result in increased lung overdistention and may compromise the lung protective effects of HFOV (Wolf and Arnold 2008).

22.1.2.3.2.2 Hemodynamic Considerations

Patients with uncorrected hypotension should be adequately volume-resuscitated and stabilized on vasopressors before the initiation of HFOV. Cardiac conditions with passive pulmonary blood flow dependency such as a Fontan circulation are a relative contraindication to HFOV, as the right ventricular preload may be further impeded with escalating mean airway pressures.

Essential to Remember

- There is a large body of evidence that HFOV is a safe strategy of ventilation allowing rapid and effective recruitment of lung volume, without significantly increased adverse events during HFOV as compared to conventional ventilation.
- HFOV is considered when conventional modes of ventilation fail to provide adequate oxygenation or adequate alveolar ventilation in pediatric patients with acute respiratory distress syndrome.
- Patients with uncorrected hypotension should be adequately volume-resuscitated and stabilized on vasopressors before the initiation of HFOV.
- Diseases with increased airway resistance (status asthmaticus, bronchiolitis, and reactive airway disease) that are associated with hypercarbia and air trapping rather than arterial hypoxemia may be relative contraindications to HFOV.

22.2 Clinical Use of High-Frequency Jet Ventilation (HFJV)

Martin Keszler

Educational Aims

- Describe historical background and current spectrum of clinical use of HFJV
- Summarize the determinants of gas exchange with HFJV
- Describe specific pathophysiologies and the principles that guide clinical use of HFJV in each condition

Initial use of HFJV in the 1980s focused on treatment of air leak, and to that end a ventilation strategy evolved that emphasized the use of minimal peak and mean airway pressures in order to facilitate resolution of the trapped air (Spitzer et al. 1989). As emphasis shifted from late rescue therapy to earlier application and as laboratory and

clinical evidence regarding the importance of the open lung concept emerged, it became apparent to a growing number of clinicians that a modification of that approach was needed (Keszler et al. 1997). Over time, we learned the importance of tailoring ventilation strategy to the underlying disease pathophysiology and the value of individualized patient care. Although different authors have divided pulmonary disorders in a variety of ways, it is useful to think of the key element in the various underlying disorder in six categories described in Table 22.1: uniform atelectatic lung disease, severe nonuniform disease, air leak syndromes, obstructive lung disease, lung hypoplasia, and restrictive lung disease.

22.2.1 Basic Principles of Controlling Gas Exchange with HFJV

The ventilator settings on the Bunnell Life Pulse ventilator are analogous to those of conventional ventilation, except that PEEP is controlled

Table 22.1 Classification of neonatal pulmonary disorders based on underlying pathophysiology

Description	Example	Key pathophysiologic feature
Uniform atelectatic disease	RDS, ARDS, diffuse pneumonia, surfactant inactivation from pulmonary hemorrhage, meconium aspiration	Short time constants, relatively uniform, prone to atelectasis, easily recruitable
Air leak syndromes	PIE, pneumothorax, bronchopleural fistula, tracheoesophageal fistula	Usually coexists with atelectatic or nonuniform disease – thus conflicting imperatives to minimize leak but avoid atelectasis. PIE adds elements of restriction and obstruction
Nonuniform disease	MAS, other aspiration syndromes, patchy atelectasis, lobar pneumonia, some patients with BPD	Highly variable regional compliance and resistance, prone to air trapping and air leak, may be complicated by pulmonary hypertension. Early stages of MAS add element of obstruction. Pathophysiology changes over time and can be highly variable
Obstructive disease	Early MAS, BPD	Increased airway resistance is the key element, typically combined with nonuniform disease and tendency for airway collapse. Prolonged time constants and air trapping are prominent features
Lung hypoplasia	CDH, PPROM, oligohydramnios, renal agenesis	Small, atelectasis-prone lungs, highly susceptible to volutrauma and air leak. Unrepaired diaphragmatic hernia adds element of restrictive disease. Pulmonary hypertension commonly present
Restrictive disease	Severe abdominal distention, severe chest wall edema, severe diffuse PIE, pleural effusion, unrepaired CDH	Lung expansion and excursion are limited by intrapulmonary or extrapulmonary space occupying lesion or external chest wall restriction. Hemodynamic compromise is common. May occur in combination with a variety of other pathophysiologies

RDS respiratory distress syndrome, *ARDS* acuter respiratory distress syndrome, *MAS* meconium aspiration syndrome, *PIE* pulmonary interstitial emphysema, *BPD* bronchopulmonary dysplasia, *CDH* congenital diaphragmatic hernia, *PPROM* prolonged premature rupture of the membranes

by the tandem conventional ventilator which also provides the option of superimposing background sigh/recruiting inflations (Harris and Bunnell 1993).

22.2.1.1 Ventilator Rate

Ventilator rate is set and displayed in “breaths”/min with a default setting of 420/min = 7 Hz, a value found in early studies to be optimal for a typical preterm infant with RDS. The ventilator rate has only a minor impact on CO₂ exchange (unless it is too high and is causing air trapping) and is normally adjusted infrequently. Like conventional ventilation, HFJV depends on passive exhalation and adequate expiratory time is necessary to avoid air trapping. The optimal rate is a function of time constants. Faster rate is appropriate and safe with uniform atelectatic disease, especially in small infants. Larger infants have longer time constants and need slower rates. Infants with obstructive lung disease (MAS, BPD) also have longer time constants. Typical rate is 420–500 for very small infants with RDS and as low as 280–320 with large infants with MAS. As RDS evolves into BPD with resulting longer time constants, ventilator rate may need to be lowered to avoid air trapping.

22.2.1.2 Inspiratory Time

The default value of inspiratory time is 0.02 s and remains unchanged under most clinical condition. The shortest possible inspiratory time allows maximum expiratory time to minimize the risk of air trapping. Only in larger infants beyond the neonatal period who are ventilated with respiratory rate ≤ 300 is a small increase in inspiratory time sometimes desirable in order to achieve larger tidal volume at maximum PIP.

22.2.1.3 Peak Inspiratory Pressure

PIP is adjusted primarily to control ventilation with a lesser effect on oxygenation. Pressure amplitude (PIP-PEEP) directly determines tidal volume for any given lung compliance. Increasing PIP with constant PEEP will improve ventilation. It is critical to recognize that improving lung compliance will result in larger tidal volume at any given pressure amplitude. Because of the

geometric relationship between V_T and CO₂ removal, even small changes in V_T can result in substantial change in ventilation. When compliance improves after lung volume recruitment or surfactant administration or for any other reason, inadvertent hyperventilation may occur rapidly – for this reason, the use of transcutaneous CO₂ monitoring is strongly encouraged. PIP has a less dramatic effect on oxygenation, because the inspiratory/expiratory ratio is very short. This means that the contribution of PIP to mean airway pressure is very small. However, substantial lowering PIP without increasing PEEP to maintain mean airway pressure may result in atelectasis.

22.2.1.4 PEEP

Adjusting PEEP is the primary means of controlling mean airway pressure and therefore oxygenation. Because the I:E ratio is typically 1:6, meaning that the bulk of each “respiratory cycle” is at the level of PEEP, airway pressure is only modestly above the level of PEEP. Consequently, PEEP values necessary for adequate mean airway pressures are higher than those used with conventional ventilation. Put another way, when changing from conventional ventilation with a typical I:E ratio of 1:2, if PIP and PEEP are kept unchanged, the mean airway pressure will drop substantially. This may be somewhat desirable when treating air leak, but when treating atelectasis-prone lungs, this will result in progressive atelectasis. Consequently, PEEP should rarely be < 6 cm H₂O and PEEP values of 10–12 cm H₂O are not unusual in infants with severe lung disease.

22.2.1.5 Background Conventional IMV

The ability to superimpose sigh breaths on top of the high-frequency ventilation breaths is a unique feature of HFJV. There are limited data to support recommendations for its use (Keszler et al. 1982). It is primarily used during initial lung volume recruitment or after suctioning or patient disconnection from the ventilator circuit, but very low rate of IMV sighs may be continued throughout to maintain recruitment of the less compliant portions of the lung. Even when optimally

recruited and made as homogeneous as possible, the lungs will have some degree of inhomogeneity due to gravitational factors. With constant distending pressure alone, an MAP high enough to maintain the less compliant portions inflated will inevitably overexpand the more compliant portions. A slightly lower MAP may be used with HFJV and very low rate of sighs (2/minute) may be helpful in periodically re-recruiting the less compliant areas. However, while used by the author for 25 years, this practice has not been systematically evaluated in clinical research. The manufacturer recommends the following approach: The IMV rate should be initially set at 5–10 breaths/min to facilitate recruitment. Once good oxygenation is achieved, the background rate can be discontinued. If oxygenation deteriorates, PEEP is insufficient to maintain lung volume and needs to be increased. If oxygenation is maintained, the background rate may remain off.

22.2.2 Tailoring Ventilation Strategy to Disease Pathophysiology

22.2.2.1 Uniform, Atelectatic Lung Disease

Babies with uniform atelectatic lung disease are ideal candidates for HFJV because of the very short time constants, thus lending themselves well to ventilation at high frequencies with little risk of air trapping. The lungs are relatively uniformly involved and can be effectively recruited (made more homogeneously inflated) with appropriate lung recruitment strategies. Optimization of lung volume is key to achieving a homogeneously aerated lung, ensuring even distribution of lung volume, preserving surfactant function, and minimizing lung injury (McCulloch et al. 1988). The advantage of HFV in general is that the use of small tidal volumes at high frequencies allows for the use of higher mean airway pressure without high peak pressure and thus allows for more effective and presumably safer alveolar recruitment. In contrast to HFOV where mean airway pressure is directly controlled, mean airway pressure with HFJV is controlled primarily by increasing PEEP on the tandem conventional

ventilator. As previously mentioned, because the inspiratory time is extremely short, mean airway pressure is only modestly higher than PEEP. Therefore, PEEP values much higher than those with which many clinicians are comfortable are required to achieve adequate lung volume recruitment. This PEEP-o-phobia has been one of the barriers to successful implementation of HFJV in the treatment of severe, uniform atelectatic disease. With HFOV where PEEP is not a set or monitored value and therefore not a concern, there is now uniform acceptance of the use of high mean airway pressure (Clark et al. 2000).

22.2.2.1.1 Rescue HFJV in Infants with Atelectatic Lung Disease

While overall HFJV use has shifted from late rescue to early rescue, as discussed above, on occasion patients transferred from other institutions need to be transitioned to HFJV when conventional ventilation is failing.

As always, an assessment needs to be made regarding the primary gas exchange defect and any coexisting problems that may require modification of the basic strategy. Typically, hypoxemia is primarily due to diffuse microatelectasis with ventilation-perfusion mismatch and intrapulmonary shunting. The imperative in this situation will be lung volume recruitment, which should improve both oxygenation and ventilation by improving V/Q matching and lung compliance. On the other hand, there may be a predominant element of pulmonary hypertension. Further increase in mean airway pressure could make the problem worse if the lungs are already well expanded or overexpanded. It is important to remember that pulmonary hypertension will always be present with severe lung disease and specifically with atelectasis. Optimizing lung inflation with volume recruitment will often resolve or at least improve pulmonary hypertension.

22.2.2.1.2 Early Use of HFJV in Infants with Atelectatic Lung Disease

When available, most clinicians will initiate HFJV long before the infant reaches an advanced severity of disease and complications ensue. Clinicians who are experienced in the use of

HFJV would typically consider changing to HFOV when PIP needed to achieve acceptable PaCO_2 and oxygenation exceeds 25 cm H_2O in infants <1,000 g and 30–32 cm H_2O in larger infants or at the first sign of PIE. These infants will likely benefit from the relative ease with which lung volume recruitment can be achieved while keeping PIP at a moderate level and improving ventilation. The primary goal here is to achieve uniform lung inflation, reduce FiO_2 , and aggressively reduce PIP once recruitment is achieved and the lung compliance improves. At this juncture it is critical to lower PIP aggressively and avoid inadvertent hyperventilation. In the past, it was routine to revert back to conventional ventilation once the infant no longer required $\text{PIP} > 20\text{--}22$ cm H_2O , but unless device availability is an issue, it is certainly feasible and possibly preferable to continue HFJV until the infant is ready for extubation to CPAP.

22.2.2.1.3 First-Line Treatment

Analogous to HFOV, some clinicians favor very early, prophylactic application of HFJV, based on the evidence from the multicenter clinical trial, (Keszler et al. 1997) believing that, with proper attention, inadvertent hyperventilation can be avoided. The general principles of treatment are identical to early rescue use, although many infants will not need aggressive lung volume recruitment.

22.2.2.2 Air Leak Syndrome

HFJV is the preferable ventilation mode for the treatment of significant PIE and severe/recurrent pneumothorax. Early users of HFJV emphasized minimal PIP and MAP, in order to facilitate resolution of the air leak, typically using PEEP of 3–5 cm H_2O . However, it soon became apparent that while the PIE resolved, the lungs became diffusely atelectatic with worsening V/Q mismatch and lung compliance, soon leading to the need for higher PIP. The unique properties of the jet ventilator make it possible to use relatively high PEEP (5–8 cm H_2O) that maintains adequate lung inflation and still allow for resolution of air leak, because the extremely short inspiratory time minimizes air passage through the point of the tissue disruption. The presence of

PIE should limit the use of aggressive volume recruitment maneuvers and encourage acceptance of higher FiO_2 requirement and PaCO_2 values. Background IMV sighs are usually discontinued when treating air leak, but exceptions to this rule may be warranted when extensive atelectasis co-exists.

22.2.2.3 Severe Nonuniform Lung Disease/PPHN

It is important to recognize that MAS is a heterogeneous condition, which evolves over time. Airway obstruction usually predominates in the early stages. Although HFJV may facilitate mobilization of secretions, the presence of particulate debris in the large airways may interfere with efficient ventilation. Thorough suctioning of the upper airway prior to initiation of HFJV is recommended. In infants in whom the surfactant inhibitory effect of meconium (Moses et al. 1991) predominates and in the subsequent inflammatory stages of MAS, HFJV is usually quite effective, because these infants have relatively uniform lung disease. It is critical to appreciate the need for lower respiratory rates (typically 280–320 bpm) in these infants who have prolonged time constants. One of the apparent, though not clearly documented, benefits unique to HFJV is the greatly increased clearance of residual meconium from the upper airways owing to the constant rotational coaxial outflow of gas along the periphery of the airway. Mean airway pressure needs to be relatively high, even in the presence of air trapping. This is because airway diameter is increased at higher MAP, minimizing the ball-valve effect of particulate meconium.

Both HFOV and HFJV are widely used in infants with PPHN and severe nonuniform lung disease who are potential candidates for ECMO. Virtually all of regional referral centers that offer ECMO have one or more types of HFV available, and anecdotally, few infants progress to ECMO without a trial of HFJV, HFOV, or both. In infants with PPHN and severe lung disease, HFJV used with the optimal lung volume strategy may be helpful in optimizing lung inflation and response to iNO. The combination of

HFJV and iNO is occasionally required for interhospital transport of critically ill infants referred for ECMO and has been successfully practiced at Georgetown University and a handful of other ECMO centers for a decade or more. Effective use of these therapies has reduced the need for ECMO for infants with MAS and PPHN to a fraction of the rate seen in the early 1990s (Conrad et al. 2005).

22.2.2.4 Restrictive Disease

The obvious physiologic rationale, supported by limited published data, has made the use of HFJV routine in these common conditions. Most clinicians will turn to HFJV when moderate to high PIP is needed to achieve adequate ventilation or whenever there is evidence of hemodynamic impairment. Aggressive alveolar recruitment is not indicated, but sufficient MAP needs to be used to maintain adequate lung volume and acceptable V/Q matching. Permissive hypercapnia and higher than usual FiO_2 targets are typically accepted in order to mitigate hemodynamic impairment. The clinical benefit is usually quite obvious, and ventilation often improves dramatically, at times leading to inadvertent hyperventilation. Worsening abdominal distention and/or chest wall edema may require subsequent escalation of support. Intravascular volume replacement and other supportive care need to go hand in hand with optimized respiratory support.

22.2.2.5 Patients with Impaired Hemodynamic Status

The benefits of HFJV in patients with impaired hemodynamic status are better documented in the pediatric and postop cardiac population, but the physiologic rationale is similar in newborn infants with a variety of underlying disorders. A trial of HFJV should be considered in any ventilated infant who, despite appropriate volume expansion and inotropic support, is exhibiting signs of impaired venous return and cardiac output. In these situations, it may be appropriate to take advantage of the ability of HFJV to achieve good gas exchange at lower MAP, compared to conventional or HFOV.

22.2.2.6 Pulmonary Hypoplasia

Anecdotally, most tertiary centers where HFJV is available routinely use this therapy as first-line treatment in infants with pulmonary hypoplasia or change over to HFJV quickly if more than modest PIP is needed to achieve adequate gas exchange with conventional ventilation. The anecdotal evidence for improved gas exchange at lower PIP with HFJV in such infants is strong and, coupled with a nonaggressive approach to ventilation, appears to have reduced the need for ECMO in this very high-risk group. Because overexpansion of hypoplastic lungs will worsen pulmonary hypertension, the general approach is to use the lowest possible PIP and MAP consistent with acceptable gas exchange, with the avoidance of lung injury and measures to control PPHN as the primary goals of therapy. It has been the author's practice to continue HFJV until pulmonary hypertension has improved and the patient is ready for surgical repair. Intraoperative and postoperative use of HFJV is physiologically attractive and supported by anecdotal experience, but its use may be dependent on the preference of the surgeon.

22.2.2.7 Bronchopulmonary Dysplasia

There is fairly extensive anecdotal experience in older infants with BPD who require rescue treatment with HFJV due to respiratory deterioration related to late-onset sepsis, necrotizing enterocolitis, or acute exacerbation of their respiratory status for other reasons. These infants require slower ventilatory rate because of their larger size and higher airway resistance but appear to respond well to HFJV when conventional ventilation is failing or requires high pressure. Because sepsis is often involved, there is often an element of restrictive disease due to abdominal distention and edema, as well as significant hemodynamic impairment. The primary pulmonary derangement may be quite variable but generally includes nonhomogeneous distribution of ventilation and variable time constants with a tendency for air trapping. The airway resistance is almost always increased, but air trapping is often made worse at lower MAP, because of airway collapse. Thus, although it may appear counterintuitive, increasing PEEP will often result in resolution of air

trapping. Because these infants may be critically ill with sepsis, their outcome requires a comprehensive approach with effective respiratory support being only one of the determinants of ultimate outcome. Elective use of HFJV in infants with moderate BPD has not been studied.

Conclusion

Although substantial body of evidence, reviewed in detail in Sect. 19.1.2. “Indications for HFJV,” is available, it is clear that clinical use of HFJV goes beyond the limited available literature. Because many of the conditions for which HFJV is used are uncommon or difficult to study or both, there will likely never be the ultimate level of evidence that would be desirable. In such circumstances, we must rely on sound pathophysiologic reasoning, carefully documented anecdotal evidence, and expert opinion, while cognizant of the potential pitfalls of such practice. It must be understood that HFJV is merely a tool in the hands of the clinician. The skill with which this tool is employed is probably far more important than how well a particular clinical indication has been studied. So long as the clinician correctly assesses the primary pathophysiologic derangement and selects the appropriate strategy to address this derangement, the patient likely stands to benefit. We must understand the operational characteristic of the ventilator and be keenly aware of potential hazards of any device that is used and not hesitate to change strategy or even abandon the use of a particular device if the patient response is not as expected.

Essentials to Remember

- Good knowledge of the factors that affect gas exchange is necessary to ensure safe and effective operation of the jet ventilator.
- A thorough understanding of the underlying pathophysiology is essential in selecting the correct strategy of ventilation.

- Achieving optimal lung volume is essential in minimizing lung injury, regardless of underlying lung disease.
- The optimal lung volume strategy is as easily applied with HFJV as with other forms of HFV.
- HFJV has unique advantages in the treatment of air leak because of the extremely short inspiratory time.
- The disease process will evolve over time and thus the strategy used requires periodic reevaluation.

22.3 Continuous Tracheal Gas Insufflation (CTGI)

Claude Danan and Xavier Durrmeyer

Educational Goals

- To understand the implications of CTGI use on flow modifications along the ventilation circuit and inside the endotracheal tube
- To identify security and monitoring device requirements associated to this technique and its possible undesirable effects
- To maintain proper gas humidification during CTGI

22.3.1 Introduction

TGI, standing for tracheal gas insufflation, and more precisely CTGI, standing for continuous tracheal gas insufflation, is a very effective technique appended to conventional mechanical ventilation (CMV) to decrease baro- and volutrauma. The objective is to wash out, with a 0.5 L/min flow at the tip of the endotracheal tube (ETT), the CO₂ trapped in the instrumental dead space in order to improve the CO₂ clearance at the alveolar level. Comparatively to

CTGI, there is no other technique able to decrease PIP to PEEP gradient or tidal volume (V_T) of 30 % in average in extremely low birth weight (ELBW) infants. These results can be higher for the most immature patients and in all situations where anatomic dead space to tidal volume (V_D/V_T) ratio is high and more efficient when arterial PCO_2 or pressures are high (Dassieu et al. 1998). The technique and results were published more than 10 years ago. Then, the small impact of CTGI in the management of tiniest babies is questionable. The reasons are of different levels:

- This ventilatory option was described between two ventilatory modes that concerned all neonatologists. One is the HFOV and the other is nasal CPAP. Both are alternatives to CMV and were supposed to decrease ventilator-induced lung injury (VILI). A lot of trials were conducted to prove the superiority of these options against CMV (Cools et al. 2009; Subramaniam et al. 2005). At the same moment, CTGI was not presented as an alternative but as an optimization of CMV, and the dream was to abandon CMV more than to optimize CMV.
- The second reason is that CTGI technique was published and was no more available to be patented. Then ventilator manufacturers were not interested, and there is no ventilator optimized commercially available with CTGI.
- The third reason is that CTGI was only described by one unit. The technical assembly proposed by this unit included security management with security devices. This objective makes the management of CTGI more complicated. Then, it was not so easy to implement the technique in other units. Moreover, FDA, taking the security concerns into account, published guidelines with the same protocol.

In this chapter, the choice is to present different solutions to install CTGI according to the local possibilities and to the severity of the patient. In all solutions, the minimum is to be able to drive 0.5 L/min of additional flow in the trachea, insuring a good humidification and the same FiO_2 than the main ventilator. These prerequisites were documented in “TGI part 2.”

22.3.1.1 CTGI Flow Input in the Trachea

TGI in adults is generally described with a catheter inserted in the ETT. In neonates, the same system is possible, but given the small size of the lumen, a catheter large enough to accept 0.5 L/min may increase resistance in the ETT and impedes suctioning without removing the catheter. The last problem is the possibility of jet lesion on the tracheal mucosa. Then, we preferred to use a specific ETT with the CTGI circuit molded in its wall. Eight capillaries are available, six of them are used for CTGI, and two others are independents and can be used for surfactant administration or tracheal pressure monitoring. Figure 22.1 shows the two options: “Option A” describes an assembly with a catheter of 1.5 mm of outlet diameter inside an ETT of 2.5 mm of inlet diameter. “Option B” describes a specific ETT [n° 990.05.1024.25 APRT, Vygon, 95440 Ecouen, France]. In this specific ETT, a single connection is used for CTGI input, and the capillary exit is located 1.5 mm above the distal end of the ETT. The inlet diameter of each capillary is 0.4 mm, then the total useful area is 0.75 mm² equivalent to a catheter with an inlet diameter of 1 mm. In option A, flow monitoring is no longer possible because the catheter cannot be inserted through the flow sensor. As specific ETT is our choice, in further description, it will be the only referred option.

22.3.1.2 Security Devices

During conventional mechanical ventilation (CMV) without CTGI, it is possible to observe a plug in the ETT. If this occurs, the ventilator will alarm and eventually stop the flow. The only risk is to have to extubate the patient. During CMV with CTGI, the problem is completely different. If the plug impedes the baby to expire through the ETT, the lung will be inflated by the continuous flow with a risk of air leaks. The risk is important because, without the possibility to discharge the flow through the ETT, a 0.5 L/min of CTGI inflates the lung by a volume of 8 ml/s. One second is an unacceptable delay to switch off the CTGI provider. Subsequently, it is mandatory to develop an automatic system able to stop the CTGI flow in the very beginning of a pressure modification

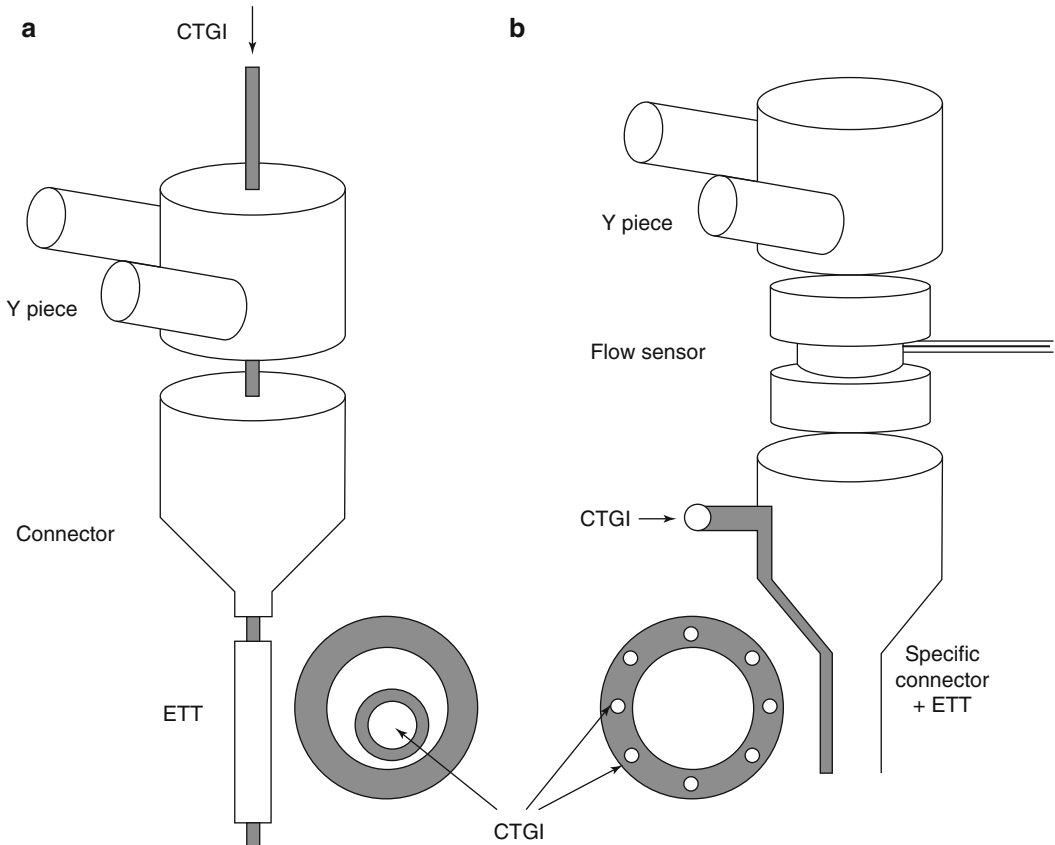


Fig. 22.1 Management of the CTGI arrival in the trachea. In option (a), a catheter to drive CTGI is inserted through an airtight membrane and passes through the Y piece, connector, and ETT. Flow sensor monitoring is no

longer possible in this assembly. In option (b), six capillary tubes, extruded in the wall, serve to convey CTGI to the end of ETT. In this option, flow monitoring is available

in the CTGI circuit. Such a system was described in the first trial in neonates (Danan et al. 1996), but some technological improvements allow simplification of the whole system. Different solutions will be described later according to different situations.

In all cases, the CTGI flow must be oriented to a valve in case of an overpressure higher than a maximum pressure set to avoid the risk of hyperinflation.

Initially, pressure in the CTGI line and tracheal pressure were controlled, and both of them were able to pilot the electrovalve (Fig. 22.2a). In our experience, the monitoring of the tracheal pressure did not add any additional safety and multiplied settings and materials. The control of pressure in the CTGI circuit is now considered as sufficient (Fig. 22.2b).

The references for material used in this assembly are blender and flowmeter (NEO2 BLEND, Bio-Med Devices, Guilford, USA), manometer (SunX-TE-21E, Panasonic EW Europe, Holzkirchen, Germany), electrovalve (VDW11-5G-1-M5-Q, SMC, Noblesville, Indiana, USA), CTGI line (RT329, Fisher & Paykel, Auckland, New Zealand) (71100.03, Vygon, Ecouen, France), and, if necessary, heater humidifier (MR850, Fisher & Paykel, Auckland, New Zealand).

22.3.1.3 Humidity Management

As it was shown in Fig. 8.65 in Chap. 8, the gases brought by CTGI flow participate largely to the alveolar gases. This participation is linked to the V_T and can rise to 100 % for the smallest V_T . Subsequently, CTGI flow has to be optimally humidified.

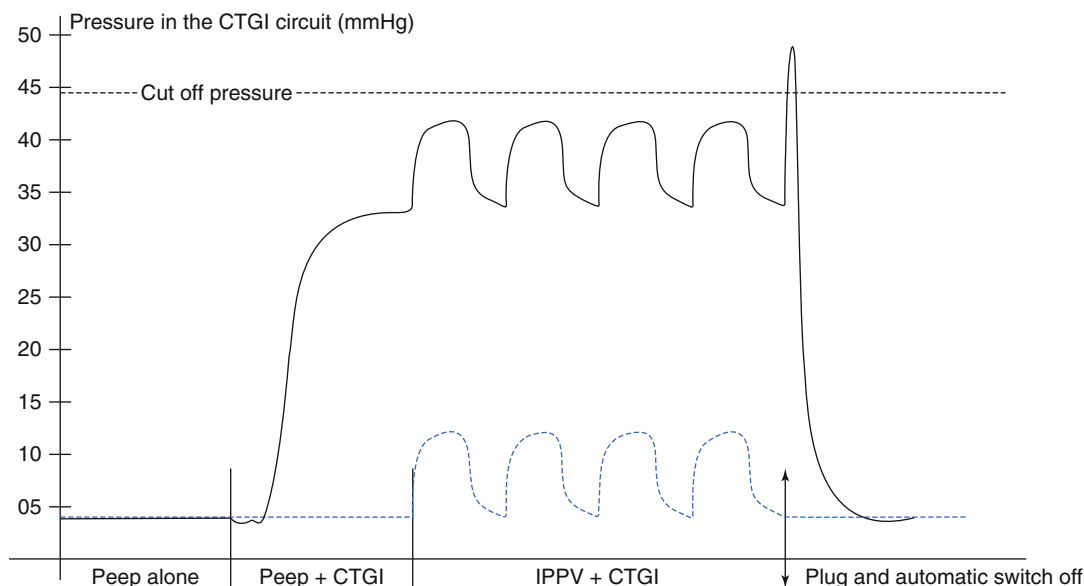


Fig. 22.2 Pressure controlled in the CTGI circuit. Pressure in the CTGI circuit (*plain line*) depends of the CTGI flow rate, the CTGI line section, and the pressure in the trachea. In this example, pressure due to 0.5 L/min CTGI flow is 30 mmHg and is added to the pressure in the trachea (4 mmHg of PEEP or 12 mmHg of PIP) to rise

until 34 mmHg with PEEP and oscillate between 34 and 42 mmHg during IPPV. A plug in the ETT activates the cutoff system set at 44 mmHg, and the pressure decreases after a maximum of 44 mmHg. Pressure monitoring by the ventilator is drawn in *dotted line*

Three options may be presented:

Option A: A 0.5 L/min of air and oxygen mixed gases are heated and humidified in a heater humidifier (Fischer & Paykel MR850, Auckland, New Zealand) before being injected in the single connection for CTGI in the specific ETT. In this option, we have to set separately the same FiO_2 in the CTGI circuit and the ventilator, and we use two different heater humidifiers: one for CTGI and one for the ventilator.

Option B: A 0.5 L/min flow is diverted from the classic-inspired line. This flow is sucked in by a pump (SerCom WBG 0221 LCB, Schiltigheim, France) downstream the heater humidifier and forced into the single connection for CTGI.

This option avoids the use of a specific blender and a specific heater humidifier for CTGI.

Option C: A 0.5 L/min of air and oxygen mixed gases is injected in a Nafion line inserted in the 30 cm inspiratory line between the heating line and the Y piece and connected to the single connection for CTGI in the specific ETT. Nafion is a synthetic polymer that is very selectively and highly permeable to water. The sulfonic

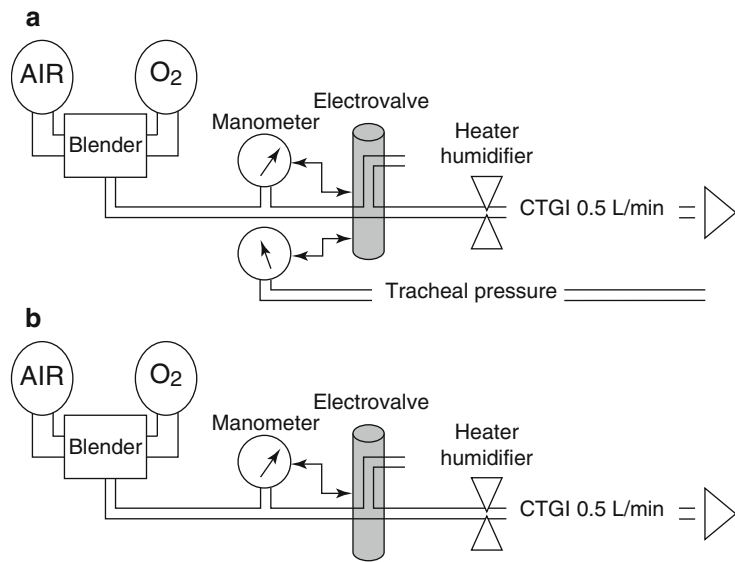
acid groups in Nafion have a very high water of hydration, so they very efficiently absorb water. Interconnections between the sulfonic acid groups lead to very rapid transfer of water through the Nafion. In this option we avoid an additional heater humidifier. It is also possible to avoid the additional blender if the ventilator is able to provide a supplemental flow with the same FiO_2 . This option was tested in a bench test with results in humidification equivalent to option B.

In all three solutions, it is possible and mandatory to insert a security device (Fig. 22.3) before the heater humidifier or before the Nafion line in option A or C and before, inside, or after the pump in option B.

22.3.1.4 CTGI Monitoring

Considering pressures, CTGI does not disturb the monitoring of the ventilator. Considering flow curves, 0.5 L/min of CTGI is detected by the flow sensor and displaces the flow curve to the bottom by 0.5 L/min without modifying the shape of the flow curve.

Fig. 22.3 Safety system for CTGI. Air and oxygen for CTGI flow are mixed at the ventilator FiO_2 and set to 0.5 L/min. Pressures in CTGI circuit and trachea (a) or only in the CTGI circuit (b) are controlled and are able to pilot an electrovalve in order to divert the CTGI flow and protect the lung in case of a tracheal plug



With a large screen, it is possible to monitor the CTGI flow measuring the offset below the zero line.

22.3.1.5 Time to Connect and Time to Disconnect

The specific targets for CTGI are the patients with high V_D/V_T ratio as is the case with the smallest and seriously restrictive patients. CTGI gives the opportunity to protect the lung from the inflammation due to volu- or barotrauma; then the best time to connect, if the patient is supposed to be sensible to CTGI, is as soon as possible, eventually at birth (Danan et al. 2008). To check the efficiency of CTGI, it is interesting to monitor transcutaneous PCO_2 (TcPCO_2). Few minutes after switching on CTGI, the TcPCO_2 decreases rapidly and allows setting a lower plateau inspiratory pressure (Dassieu et al. 1998). At the beginning, CTGI is very efficient, but during the evolution, the disease becomes less restrictive and the V_D/V_T ratio will be modified. Then we have to anticipate the time to disconnect the patient from CTGI. The best way is to make a disconnection test and to compare the PCO_2 or TcPCO_2 during CTGI and few minutes after disconnection. If the PCO_2 is not modified more than 10 %, the benefit will not be interesting for the patient, and the CTGI should be permanently switched off.

22.3.1.6 Warning and Limitations of the CTGI Technique

- Using CTGI in rescue: Using a blender set at the same FiO_2 than ventilator and a heater humidifier as it is described in Fig. 22.4a, CTGI is possible, for instance, for a tiny baby with intolerably high PCO_2 in spite of high pressures and no HFOV available. It is important to keep in mind the risk of hyperinflation in case of ETT plug and to verify the ETT lumen frequently by suctioning.
- Using CTGI in routine: CTGI during days is possible but security device is mandatory.
- Tracheal suctioning: With a catheter for CTGI inserted in the ETT, we have to move the catheter, suction, and place again the catheter. With the specific Vygon ETT, it is possible to suction whenever it is necessary. During suctioning, the CTGI flow supplies oxygen and facilitates breathing. Subsequently, there is less bradycardia or hypoxemia. With security device, the activation of alarm indicates the need for suctioning and sometimes is activated by suction itself.
- Using a pump as CTGI flow provider (Fig. 22.4b): Two problems are difficult to deal with. One is the noise as the best location for the pump is inside the incubator; the other is the difficulty to sterilize the device between two patients.

- **Monitoring:** As it is shown in Fig. 22.5, the pressure curve on the ventilator screen is not modified by CTGI. When we have monitored the tracheal pressure during CTGI, we have noticed that the pressure curve is lift of 0.85 mmHg for 0.5 L/min of CTGI flow rate. Then we have to take into account for both the PIP and PEEP an additional 1 mmHg. For instance, if we have set 10 mmHg for PIP and 3 mmHg for PEEP, we have to consider that the actual values are, respectively, 11 and 4 mmHg. The flow curve is not modified but with an offset of 0.5 L/min increasing artificially the V_T . To measure the real V_T , it is possible to stop CTGI for a few seconds and to note the real V_T .
- **Influence of CTGI on ventilatory modes and options:** Synchronized ventilation is possible, but not volume targeted ventilation. Conversely, tracheal CPAP with CTGI is possible as we can consider the instrumental V_D completely erased by CTGI.

Conclusion: CTGI needs to be evaluated in large multicentric studies, but at this moment, there is no ventilatory mode or option available on our ventilators able to be as effective as CTGI. If the use of CTGI is indicated, it must be managed preferentially with a security device, presented in Fig. 22.3b, able to switch off automatically the CTGI flow and to open an electrovalve to accel-

erate the diminution of the pressure in the CTGI circuit. Electrovalve opening activates an alarm and a reset reactivates the CTGI flow after checking the ETT lumen is free of plug.

Conclusion

CTGI is a very effective adjunct to conventional ventilation. If new ventilators were upgraded with CTGI, with specific monitoring and security, CTGI would become uncontestable. Before this eventuality, for those who are convinced by the benefit of this technique, we present in this chapter different modalities to manage CTGI according to the conditions of the patient or the local possibilities in each unit. The authors highlight the risk of hyperinflation if CTGI is managed without appropriate security device.

Essentials to Remember

- CTGI is very effective for PCO_2 lowering and has an almost immediate effect.
- Pressure monitoring inside the tracheal tube and an automatic switch-off device are mandatory to provide safety in current clinical use. Otherwise, patients are exposed to a risk of overinflation possibly creating air leaks.

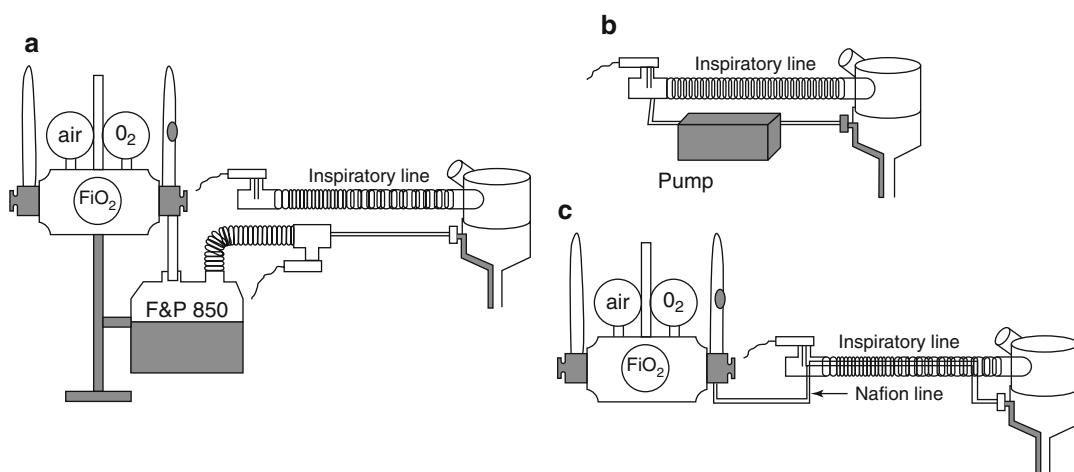


Fig. 22.4 Different options to insure humidification in CTGI flow. Three options to provide appropriate humidification of CTGI flow. “Option a” is the easiest but needs an additional blender and an additional heater humidifier with an F&P RT329 circuit (see Fig. 22.3). “Option b”

requires a pump that is not commercially available but easy to built. “Option c” may be the option for the future as it does not need non-patented device and avoids an additional heater humidifier

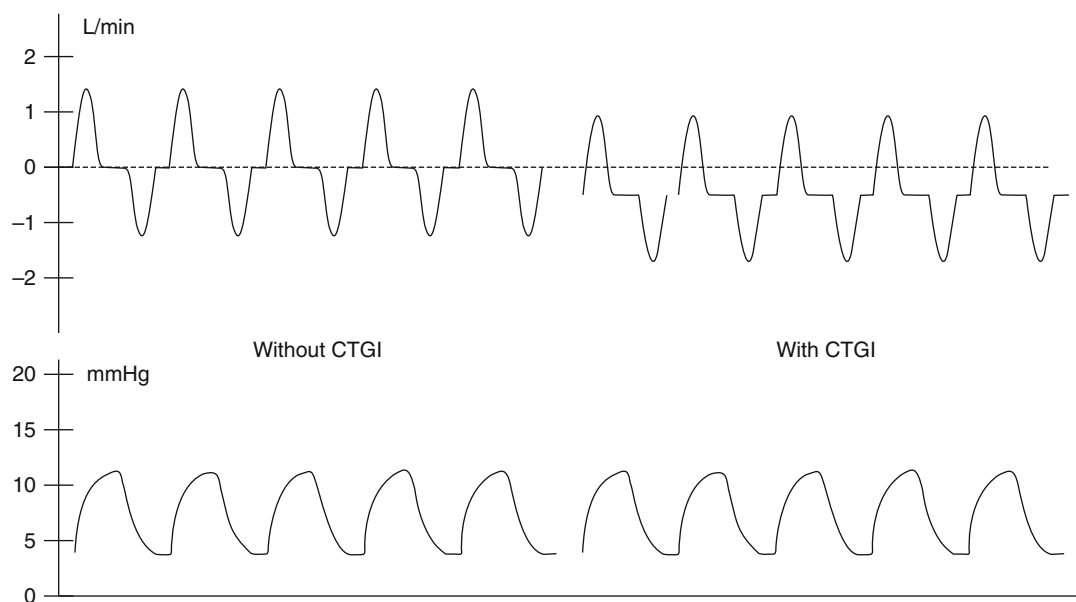


Fig. 22.5 Flow and pressure curves monitored by the ventilator without and with CTGI. During CTGI on the right side, the pressure curve is not modified. If we consider the flow curve, expired V_T (negative part of the curve) seems to be increased by CTGI. The real V_T is not

modified but CTGI flow participates to the lung inflation during inspiration decreasing the positive part of the curve and is driven from the bottom of the ETT to the Y piece during expiration increasing the negative flow detected by the flow sensor

- Proper humidification of tracheally insufflated gas is necessary to avoid irritation of airways and alveoli.

22.4 Clinical Use of Liquid Ventilation

Thomas H. Shaffer, Kevin Dysart
and Marla R. Wolfson

Educational Aims

- Characterize the mechanisms by which liquid perfluorochemical benefits infants with severe pulmonary distress
- Outline the patient populations that have been treated with liquid ventilation techniques

Currently there is no clinical use of perfluorochemical liquid ventilation in medical practice, except compassionate use for “in extremis”

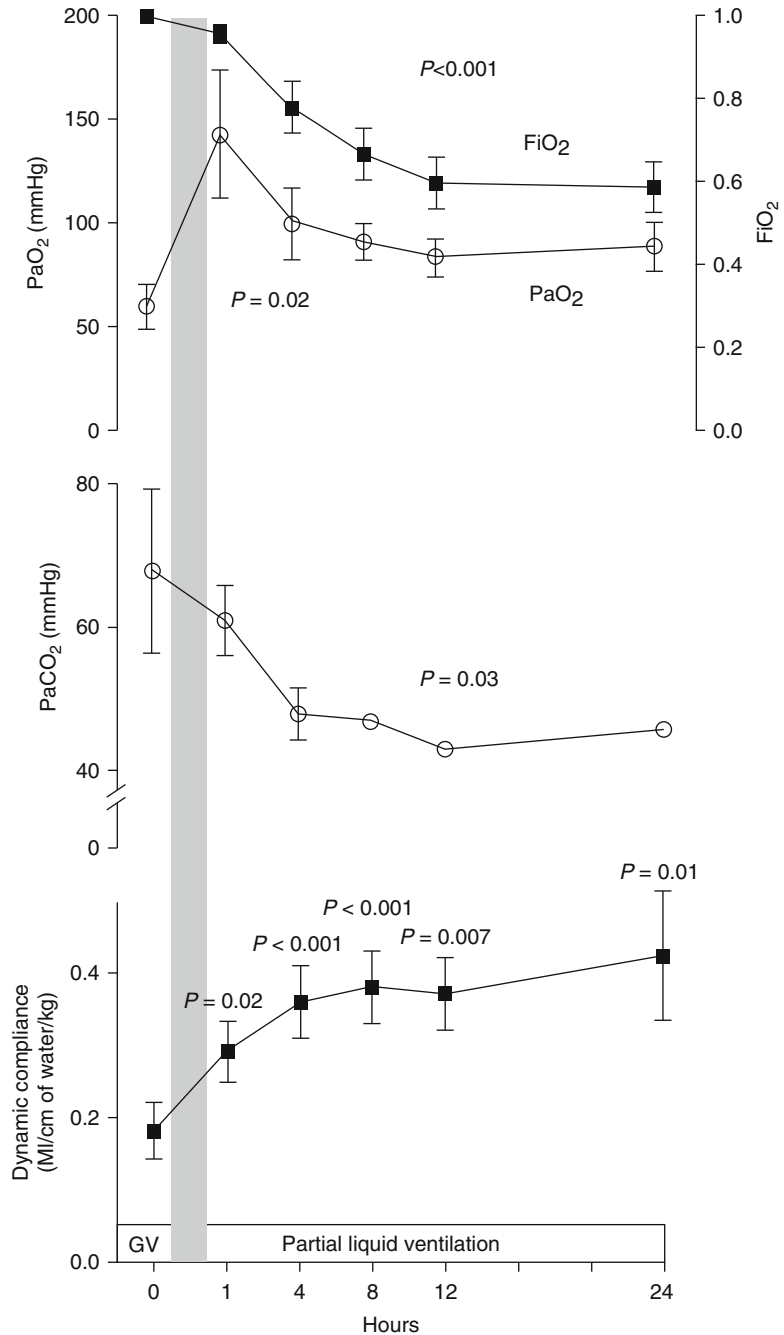
cases. Clinical trials conducted throughout the decade of the 1990s have not been continued through the last decade. A combination of factors led to the cessation of clinical trials in newborns in favor of clinical trials conducted in adults. The following sections will discuss the potential use of liquid ventilation in populations of newborns most likely to benefit from the therapy.

22.4.1 Very Low Birth Weight Infant (VLBW)

While there is no regulatory-approved clinical use of perfluorochemical liquid ventilation in the management of VLBW infants, it is in this population that the therapy has been most widely investigated in both animals and human neonates.

Multiple animal studies as well as early trials in critically ill neonates have demonstrated clear promise for the therapy in the treatment of respiratory distress syndrome (Moskowitz et al. 1975; Shaffer et al. 1983, 1984; Wolfson et al. 1992; Richman et al. 1993; Leach et al. 1993)

Fig. 22.6 Mean ($\pm$ SE) values for arterial oxygen tension (PaO_2), arterial carbon dioxide tension ($PaCO_2$), the fraction of inspired oxygen (FiO_2), and dynamic compliance during gas ventilation, and the initial 24 h of partial liquid ventilation in the ten infants who completed the study. *P* values are for the comparisons between partial liquid ventilation and gas ventilation. The gray bar denotes the period during which the liquid fraction residual capacity was established (Reprint from Leach et al. (1995))



Reestablishing a liquid-liquid interface at the alveoli reduces surface tension while minimizing both volutrauma and barotrauma.

These factors make it likely that liquid ventilation will be successful in altering the current natural course of RDS for this at-risk group.

Animal models of RDS uniformly demonstrate marked improvements in oxygenation and

ventilation in the liquid ventilation treatment arms.

Not only are there dramatic improvements in clinical variables of gas exchange, but there is clear evidence of histologic improvement as well (Wolfson et al. 1992).

Consistent with these animal experiments, the infants treated in early rescue trials demonstrated

significant improvements in oxygenation and ventilation (Greenspan et al. 1989, 1990; Leach et al. 1995) (Fig. 22.6).

It is in this group of infants that liquid ventilation offers an opportunity to change the course of RDS, but further clinical studies are needed to define which infants in this population will most benefit from therapy.

22.4.2 Extracorporeal Life Support

Previous clinical trials have investigated the use of PFC liquid ventilation in infants that require extracorporeal life support (ECLS). The infants that have been treated to date have all demonstrated severe illness, even for this population (Gross et al. 1995; Hirschl et al. 2003)

While none of the past research conducted utilizing PFC liquid ventilation in newborns requiring ECLS answered the questions necessary to understand the future clinical use of therapy, they do provide some guidance in understanding the potential combination of both therapies.

Moving forward, infants with initial diagnoses such as congenital diaphragmatic hernia (CDH), sepsis, and meconium aspiration syndrome could all benefit from the combination of the two therapies.

Infants whose courses have been complicated by the need for ECLS and are failing to improve may benefit from the use of PFC liquid ventilation.

The ability of the liquid media to improve oxygenation, ventilation, alveolar recruitment, and ventilation-perfusion matching may lead to more successful weaning from the ECLS and improve overall survival, especially in groups with typically poor outcomes.

22.4.3 Bronchopulmonary Dysplasia

Infants with bronchopulmonary dysplasia (BPD) present an interesting subpopulation in whom perfluorochemical liquid ventilation (PFC) may prove useful. While no previous clinical trial has investigated the use of PFC liquid ventilation in a similar group, the disease process lends itself to the approach of breathing a liquid media.

Infants with BPD suffer a disease process characterized by disordered alveolar development and a heterogeneous mixture of lung units characterized by air trapping and overdistention in combination with atelectatic lung units. PFC liquid ventilation potentially offers the ability to improve oxygenation and ventilation not only through recruiting atelectatic lung units but also through improving the overdistention of the air-trapped lung segments.

In combination with a short-term improvement in gas exchange with the clinical use of PFC liquid ventilation in this population, there is the potential benefit of minimizing ongoing volutrauma and barotrauma.

The use of PFC liquid ventilation in this population for a period of time may offer short-term stabilization as well as a period of time in which the negative consequences of positive-pressure ventilation are interrupted potentially allowing the diseased lung a period of time to begin healing.

While we recognize that many of these clinical uses are still merely hypothetical, they may represent only a small fraction of the potential future uses. It is imperative that future clinical trials be designed to define the populations in whom the clinical use of PFC liquid ventilation will be most beneficial.

Essentials to Remember

- Based on physiological responses, liquid ventilation has shown greatest clinical promise in VLBW, CDH, sepsis, and meconium aspiration syndrome infants.
- Infants with BPD are characterized by disordered alveolar development and a heterogeneous mixture of lung units characterized by air trapping and overdistention in combination with atelectatic lung units. PFC liquid ventilation potentially offers the ability to improve oxygenation and ventilation not only through recruiting atelectatic lung units but also through improving the overdistention of the air-trapped lung segments.

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Part VIII

General Management of the Ventilator-Supported Patient

The Prone Position in Acute Lung Injury

23

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Educational Goals

- To describe the physiologic effects of prone positioning on normal and diseased lungs
- To review the outcomes of clinical studies evaluating prone positioning as a treatment for acute lung injury and acute respiratory distress syndrome in adults and children

- To discuss the indications and contraindications for prone positioning in pediatric patients
- To highlight the steps clinicians can take to use prone positioning safely in critically ill children

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23.1 Introduction

Refractory hypoxemia is a characteristic feature of severe ARDS. Over the last 30 years, prone positioning is one intervention clinicians have used to improve oxygenation in these patients. Prone positioning improves oxygenation via better ventilation-to-perfusion matching and improved lung mechanics while reducing the potential for ventilator-associated lung injury. In both pediatric and adult studies, prone positioning has been found to be a safe and relatively noninvasive maneuver for patients with ARDS. Though prone positioning clearly improves oxygenation, clinical trials have not demonstrated improvements in survival or morbidity.

23.2 Basic Principles

It has long been known that changes in body position alter lung volumes, gas exchange, and perfusion. In 1933, Beams and Christie first noted that lung vital capacity was lower when in the supine

position than in the upright position (Christie and Beams 1933). That same year, Hurtado and Frey found that the functional residual capacity (FRC) was also lower in the supine position (Hurtado and Frey 1933). Later, in 1955, by studying subjects using helium washout, Blair and Hickam showed that these positional changes were also associated with changes in gas mixing (Blair and Hickam 1955). The first description of the potential for prone positioning to reverse these effects came in 1961, when Moreno and Lyons studied lung volumes in patients transitioning from sitting to supine and prone positions. They demonstrated that FRC was higher in the prone position than in the supine position (Moreno and Lyons 1961). Notably, a subsequent study comparing supine and prone positioning in pediatric patients has revealed no difference in FRC (Numa et al. 1997).

Prone positioning was first proposed as a therapeutic modality for improvement of lung mechanics in 1974, when Bryan described improved oxygenation in patients under general anesthesia and neuromuscular blockade when placed prone (Bryan 1974). Several investigators subsequently demonstrated that prone positioning improved oxygenation in patients with ARDS (Douglas et al. 1977; Piehl and Brown 1976). Over the last 30 years, there has been increasing interest in prone positioning, which has been used in all age groups to improve oxygenation and respiratory mechanics.

23.3 Physiologic Effects

23.3.1 Normal Lungs

In normal lungs, changes in body posture affect oxygenation by (1) changes in distribution of alveolar inflation and ventilation, (2) by differences in regional perfusion, and (3) by changes in lung and chest wall mechanics. When supine, alveolar inflation and ventilation are preferentially distributed to nondependent ventral regions. The difference in the transpulmonary gradient between dependent and nondependent regions explains the difference in alveolar expansion between the regions. The transpulmonary

gradient, the difference between the alveolar and pleural pressures, is higher in the ventral regions compared to dorsal regions of the lung in the supine position, which preferentially favors ventilation of ventral (nondependent) lung.

The difference in the transpulmonary gradient is due to several factors, including lung weight, heart mass, diaphragm displacement by intra-abdominal contents, and chest shape. The force of gravity and the mass of dependent lung regions both act to favor alveolar distention and increased transpulmonary gradient in nondependent lung areas. Under physiologic conditions, the mass of the heart also contributes by compressing underlying lung tissue (Hyatt et al. 1985). When patients are supine, the weight of the abdominal contents may compress dependent regions of the diaphragm and therefore increase pleural pressure, decreasing the transpulmonary gradient. This is particularly true in patients under general anesthesia and neuromuscular blockade (Froese and Bryan 1974).

When a patient is moved from the supine to the prone position, alveolar ventilation redistributes from the ventral regions to the dorsal regions. In addition, prone positioning results in a more homogeneous transpulmonary pressure gradient when compared to the supine position (Mutoh et al. 1992). This change in the distribution of transpulmonary pressure is due to (1) alteration in the lung weight gradient, (2) reductions in the mass of the heart transmitted to underlying lung, (3) decreased intra-abdominal pressure in the prone position which decreases cephalic displacement of the diaphragm, and (4) changes in regional chest wall mechanics and shape in the prone position (Pelosi et al. 2002).

In 1964, West and colleagues observed that lung perfusion increases gradually from nondependent to dependent lung regions (West et al. 1964). Classically, the “gravitational theory” was used to explain this observation, which proposed that perfusion increases steadily in more dependent lung regions solely due to the effects of gravity. The prone position could therefore reverse this gravitational gradient and redistribute perfusion to the better-ventilated ventral lung. Recent studies have challenged this notion and suggest that gravity plays only a minor role in the

redistribution of perfusion in the lung. In fact, it appears that more dorsal lung regions are always preferentially perfused due to the geometry of the pulmonary vasculature (Glenny and Robertson 1991; Glenny et al. 1991; Wiener et al. 1990). This observation increases the likelihood that prone ventilation reduces shunt by changes in regional ventilation rather than to changes in pulmonary perfusion.

As a child matures, the thoracic shape, compliance, and deformability change significantly. In the newborn, the ribs extend horizontally, producing a circular chest shape. The newborn's rib cage is highly compliant and easily deformable, predisposing the newborn to paradoxical movement of the chest wall during inspiration which interferes with the mechanical coupling of diaphragmatic and chest wall movement. The high ratio of chest wall compliance to lung compliance (6.7:1) exaggerates the magnitude of the paradoxical motion between the caudal surface of the lung (driven by the diaphragm) and the remaining lung (driven by the rib cage) (Gerhardt and Bancalari 1980). In the older child, caudal inclination of the ribs increases both the efficiency of the thoracic mechanics and intrathoracic volume. In the adult, the thorax has a smaller relative anteroposterior diameter, and increased intrathoracic volumes are produced by the "bucket handle" or the "pump handle" effect of costal elevation during inspiration. These changes in the thoracic shape, along with the increased effect of gravity in the upright position, the development of the thoracic musculature, and the mineralization of bone, all result in decreased chest wall compliance and deformability in adults. Total respiratory compliance decreases progressively from 5 to 16 years of age, and the decrease in chest wall compliance prevents paradoxical motion of the chest wall during inspiration, improving mechanical coupling of the diaphragm and chest wall (Sharp et al. 1970).

Newborns, especially preterm infants, may be more prone to fatigue of respiratory muscles because of the increased workload imposed by the characteristics of their chest wall. Indeed, the work required to expand the chest wall may be up

to four times the work required to produce movement of the lung (Heldt and McIlroy 1987). Lateri and Sly demonstrated that, compared with older children, infants had disproportionately higher respiratory system compliances, as an influence of chest wall composition after adjusting for the effects of lung volume (Nicolai et al. 1993). In addition to the effect of the compliant chest wall on work of breathing, there is also a significant effect on the airways which compromises the efficiency of gas exchange. The reduced outward recoil of the chest wall during end expiration in infants limits the distending pressure in the pleural space which results in airway collapse, atelectasis, decreased functional residual capacity, and impaired gas exchange (Stocks 1999).

Prone positioning has a significant impact on respiratory mechanics in healthy children. In a study of ten healthy infants undergoing surgery for clubfoot, Cox and colleagues recorded pulmonary mechanics in the supine and prone positions. The study, which was the first to examine the physiologic effects of prone positioning in healthy infants, found that both static and dynamic respiratory system compliances were significantly lower in the prone position compared to the supine position. This was not associated with any impairment of gas exchange (Cox et al. 2001).

23.3.2 Diseased Lungs

There are a number of physiologic benefits when prone positioning is utilized in patients with lung diseases such as ARDS, including improvement in V/Q matching, a more homogeneous transpulmonary pressure gradient, improvement of alveolar recruitment, better respiratory mechanics, and the potential for reduced ventilator-induced lung injury (VILI).

Computed tomography (CT) scans of lungs affected by ARDS have revealed that alveolar inflation follows a gravitational gradient, with nondependent regions exhibiting more expansion than dependent regions (Fig. 23.1). This suggests that more dependent regions of the lung collapse under the lung's own weight and

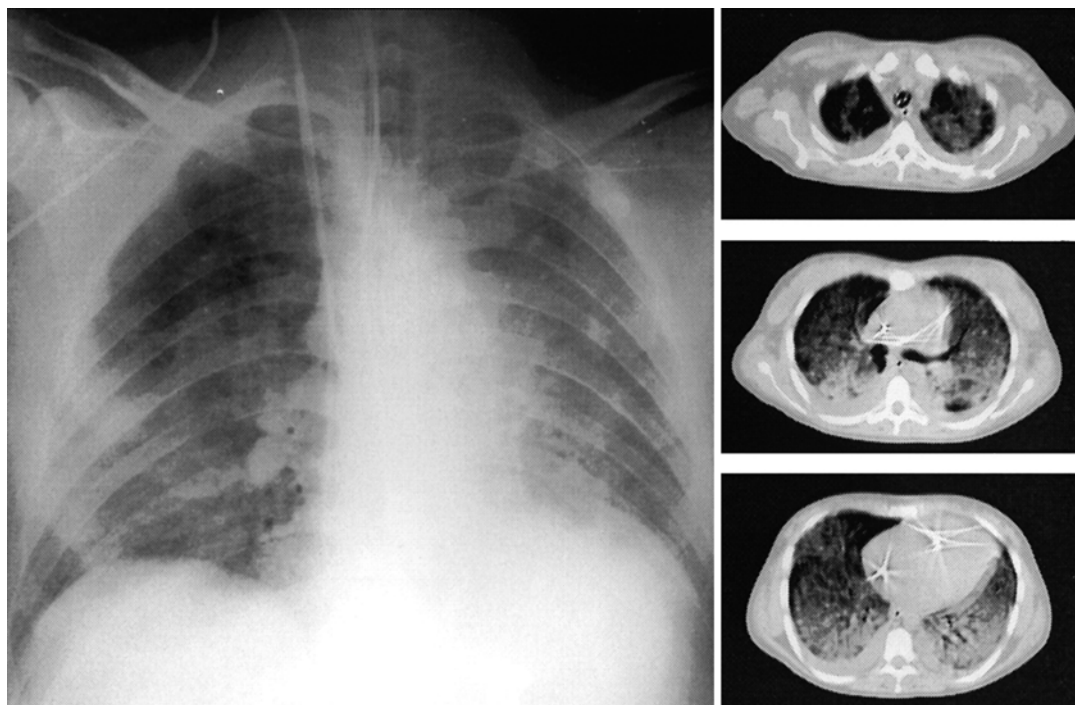


Fig. 23.1 CT scans—apex, hilum, and base—in ARDS from sepsis. Images were taken at 5 cm H₂O end-expiratory pressure. The CT scans show heterogeneous disease

and both the craniocaudal and sternovertebral gradients (From Gattinoni et al. (2001))

do not participate effectively in gas exchange. The atelectasis-prone dependent regions of the lung are therefore more likely to endure repetitive collapse and inflation (atelectrauma) during mechanical ventilation. At the same time, dependent lung regions have preferentially more perfusion than nondependent regions. The result is a mismatch in ventilation and perfusion. Prone positioning dramatically alters the distribution of alveolar ventilation and leads to enhanced ventilation-perfusion matching. Transpulmonary pressure is more evenly distributed, resulting in a more homogeneous distribution of alveolar inflation. This, in turn, allows improved ventilation of dorsal regions. Perfusion of the lung in the prone position is more homogeneous than in the supine position (Lamm et al. 1994). Overall, the result of prone positioning is an increase in the V/Q ratio. This was shown by Pappert and colleagues who administered pressure-controlled ventilation in the prone position for 2 h–12 adult patients with ARDS (Pappert et al. 1994). Using the multiple

inert gas elimination technique (MIGET), the authors recorded continuous ventilation-perfusion ratios. Within 30 min of prone positioning, eight patients, the responders, showed improved oxygenation, which they attributed to reduced perfusion to shunt regions and resultant increase in the V/Q ratio. The change in perfusion from non-ventilated lung regions to those with normal V/Q ratios was thought to be due to the redistribution of ventilation to previously collapsed regions of the lung.

Prone positioning may have a variable effect on improving oxygenation depending on the underlying recruitment status of the patient's alveolar units. Recruitment normally progresses from ventral to dorsal and from cephalad to caudal (Puybasset et al. 1998). In light of this, one might imagine that prone positioning is less likely to have the same benefit in a derecruited lung as it might in a recruited lung. One study recently examined the effect of prone positioning on alveolar recruitment and oxygenation in a

cohort of adult patients with ARDS (Guerin et al. 1999). The investigators found a correlation between change in oxygenation and the recruited lung volume. They hypothesized that one of the mechanisms by which prone positioning improved oxygenation was recruitment. Another study examined the effect of prone positioning on enhancing the outcome of recruitment maneuvers in patients with ARDS. The authors concluded that cyclical sustained inflations during ventilation in the prone position may produce optimal lung recruitment (Pelosi et al. 2003b). Oczenski and colleagues demonstrated a prolonged improvement in oxygenation after performing a recruitment maneuver in patients who were maintained in the prone position for 6 h (Oczenski et al. 2005). These studies support the hypothesis that redistribution of ventilation and enhanced alveolar recruitment is the mechanism of improvement in oxygenation in patients with ARDS. This may have important implications in patients with extrapulmonary ARDS, whose lungs may be more responsive to standard recruitment measures (Lim et al. 2003; Pelosi et al. 2003a). Because patients with secondary ARDS may have more recruitable lungs than those with primary ARDS, they are more likely to respond to prone positioning.

In supine patients, the anterior chest wall is normally more compliant than the posterior chest wall as there is little impediment to anterior movement of the rib cage. When patients are transitioned to the supine position, this anterior chest wall compliance is impeded by the patient's bed, and the posterior chest wall has a relatively improved compliance. In a study of 16 adults with ARDS, Pelosi and colleagues proposed that these relative differences in chest wall compliance explain the improved alveolar ventilation of dependent lung areas when patients are supine (Pelosi et al. 1998).

Another potential benefit of utilizing the prone position in ARDS is that of limiting ventilator-induced lung injury (VILI). VILI involves various mechanisms, including overdistention through excessive volume delivery ("volutrauma") or transpulmonary pressure ("barotrauma") and the phenomenon of alveolar

collapse and reinflation ("atelectrauma"), which may lead to a local and systemic inflammatory reaction (Slutsky 1999). In a recent animal model, Valenza and colleagues demonstrated a delay in the progression of VILI with prone positioning (Valenza et al. 2005). Recent animal studies with preinjured lungs ventilated with large tidal volumes demonstrated less histopathologic injury in the prone versus the supine position (Broccard et al. 1997, 2000). In addition, they found that in the supine position, lung injury was primarily located in the dependent lung areas, while in the prone position, lung injury was more homogeneously distributed. These preclinical studies uniformly suggest that the prone position may act to protect the lung from developing VILI, as well as to slow the progression of existing lung injury.

23.4 Effectiveness and Outcome

Most of the large clinical trials of prone positioning in ARDS have been performed in the adult population. In the neonatal and pediatric populations, several investigators have examined small cohorts of patients. These studies as well as a recently published randomized, controlled trial in pediatric patients are summarized in Table 23.1. The initial reports of prone positioning in pediatrics were limited by nonrandom assignment of prone positioning for variable time periods in a heterogeneous population. These limited reports, along with a lack of uniform guidelines to perform prone positioning safely and effectively, led to reluctance among pediatricians to perform this maneuver. Yet, these initial reports did describe dramatic improvements in oxygenation soon after children with ALI/ARDS were placed in the prone position. The improvement in oxygenation and the resultant potential to reduce inspired oxygen concentrations as well as airway pressures have spurred continued study of prone positioning in pediatrics.

Key components to consider in the studies on pediatric prone positioning to date include patient selection, the timing and duration of prone positioning, and outcome measurement. Patient

Table 23.1 Pediatric studies: prone position

Reference	Year	Level of evidence	Type of study	# of pts	Entry criteria	Timing > lung injury (mean)	Frequency of PP (# of cycles)	% of time in PP	Duration in PP	Duration in SP	Responders	Adverse effects	Outcomes measured
Murdoch and Storman (1994)	1994	3b	1-center Prospective case series	7	ARDS	4.5 days	1	–	0.5 h	0.5 h	100 %	–	CO, HD variables, DO ₂
Numa et al. (1997)	1997	3b	1-center Prospective case series	30	Intubated pts Control = 10 Obstructive = 10 Restrictive = 10	12 days	1	–	70 min	Rest of the day	NA	–	ABG, FRC, C _{RS} , R _{RS}
Curley et al. (2000)	2000	3b	1-center Prospective case series	25	ALI/ARDS	<19 h	1–12	47 %	20 h/day	4 h/day	84 %	St II Skin ulcers in 24 %	PaO ₂ to FiO ₂ ratio, mortality (study, 28-day), adverse effects, COMFORT score
Kornecki et al. (2001)	2001	3b	1-center Prospective case series	10	ARF OI > 12 FiO ₂ > 0.5 For 12 h		1		12 h/day	12 h/day	90 %	Facial edema in 30 %	HD, OI, Static C _{RS} and R _{RS}
Casado-Flores et al. (2002)	2002	3b	1-center Prospective case series	23	ALI/ARDS	56 h	2–14	36 %	8 h	8 h	78 %	–	PaO ₂ to FiO ₂ ratio
Haefner et al. (2003)	2003	4	1-center Retrospective cohort	63	ECMO for resp failure	–	15 position changes	–	–	–	NA	–	Adverse effects recorded
Relvas et al. (2003)	2003	4	1-center Retrospective chart review	40	ARDS	107 h	Variable	–	>20 h (n = 37)	–	–	–	OI, PaO ₂ to FiO ₂ ratio,
Curley et al. (2005)	2005	1b	Randomized, multicenter study	102	ALI/ARDS	<48 h	Up to 7		20 h/day	4 h/day			Ventilator-free days, mortality, time to recovery from lung injury, organ-failure-free days, functional outcome

selection for prone positioning is challenging and may be integral to understanding the true benefit and correct application of the intervention. One important factor in patient selection is that acute lung injury from different etiologies does not share the same morphological, mechanical, and clinical characteristics. For years, investigators of adult ALI and ARDS have debated the clinical significance between pulmonary and extrapulmonary etiologies of lung injury (Callister and Evans 2002; Pelosi and Gattinoni 2001). Some assert that the two conditions are different entities, with different pathophysiology, radiographic appearance, and respiratory mechanics (Pelosi et al. 2003a). The two entities may also have different responses to prone positioning. Indeed, Pelosi and colleagues have reported that secondary ARDS, with associated diffuse atelectasis, may be more responsive to prone positioning (Pelosi et al. 2002). Primary ARDS, characterized by altered *lung* elastance, may not benefit from strategies such as increased PEEP, lung recruitment, and prone positioning, compared to patients with secondary, or extrapulmonary, ARDS, which may be characterized more by altered *chest wall* elastance. It is important to note, however, that the difference in the two conditions in terms of the impact of different therapies is unknown. Indeed, a recent study revealed no difference in lung functional assessment 6 months after hospital discharge in adult patients with pulmonary versus extrapulmonary ARDS (Suntharalingam et al. 2001).

The overall length of mechanical ventilation is important when considering patient selection in studies on prone positioning. In 1997, Numa and colleagues examined the effect of prone position on functional residual capacity (FRC), oxygenation, and respiratory mechanics in mechanically ventilated children with restrictive and obstructive lung disease and in controls (Numa et al. 1997). The investigators found a pattern of increased FRC in the prone position in each of the three subgroups, though this improvement did not reach statistical significance. There was no significant improvement in oxygenation in any of the groups. One important caveat to the study is that the authors enrolled patients after

prolonged periods of mechanical ventilation (up to 2 weeks), and this may have influenced the physiologic effects that prone positioning had on this population.

Outcome measures are important to consider when evaluating studies on ARDS. Traditionally, the degree of oxygenation has been the main surrogate of the severity of lung injury in studies on ARDS. This holds true in studies evaluating the role of prone positioning. Pediatric studies evaluating the role of prone positioning in ARDS have used indices of oxygenation such as the oxygenation index (OI) and the $\text{PaO}_2/\text{FiO}_2$ (P/F) ratio as outcome measures (Casado-Flores et al. 2002; Curley et al. 2000; Kornecki et al. 2001). In a prospective case series of 25 pediatric patients with ARDS, an immediate and cumulative improvement in oxygenation was demonstrated after prone positioning (Curley et al. 2000). The study included patients from 2 months to 17 years that were enrolled within 19 h of meeting entry criteria. Patients were placed prone for 20 h each day and returned to the supine position for 4 h, accounting for 47 % of the time on mechanical ventilation. Indices of oxygenation, including P/F ratios and OI, are shown in Fig. 23.2 at four time points in the first 24 h of prone positioning. Both P/F ratio and OI significantly improved at both 1 h and up to 19 h after prone positioning. Based on the response to prone positioning in the first 24 h, the investigators then classified patients as immediate responders ($n=11$, 44 %) and immediate nonresponders ($n=14$, 56 %). In the immediate responders, oxygenation improves early and is sustained during the prone period (Fig. 23.3). Even after this subgroup of patients (immediate responders) returned to the supine position, they exhibited preserved improvement in oxygenation. Nonresponders were found to have a delayed and non-sustained improvement in oxygenation. The authors reported an overall 84 % rate of response to prone positioning in this population of children. Casado-Flores and colleagues also showed an improvement in oxygenation with prone positioning in a population of 23 children with ARDS (Casado-Flores et al. 2002). In contrast to the previously summarized study, they showed that the improvement in oxygenation

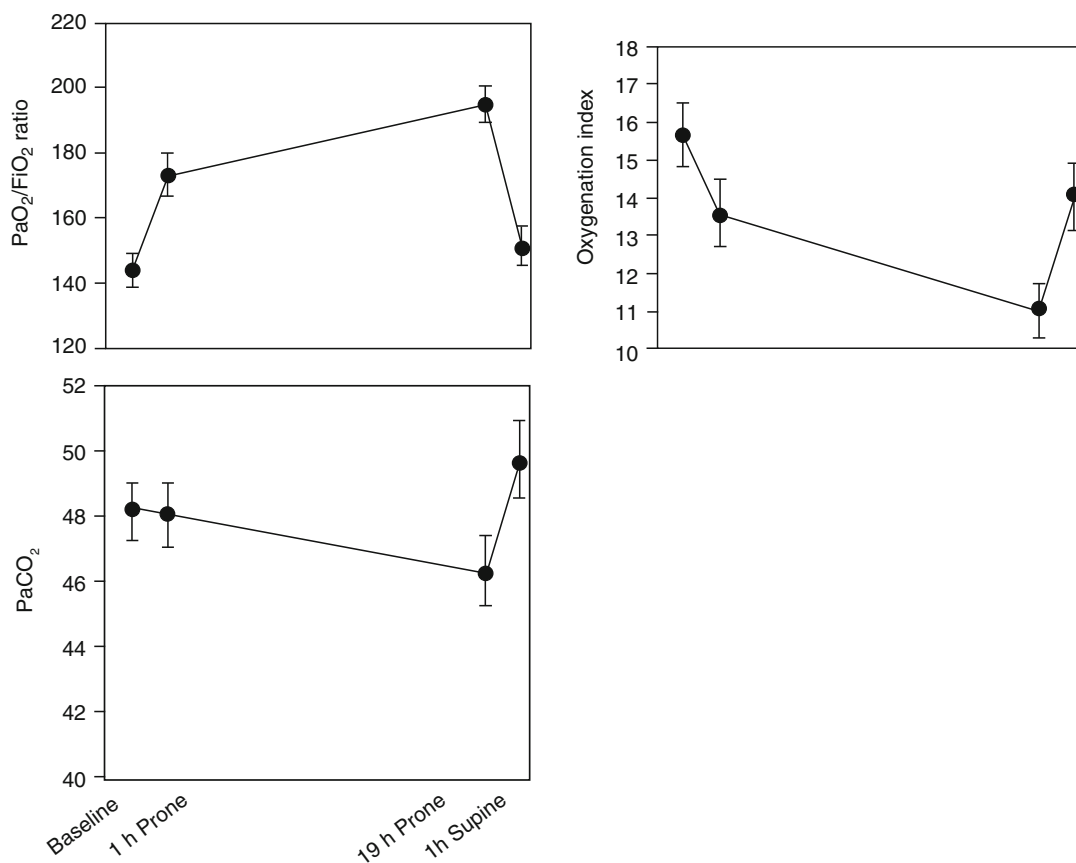


Fig. 23.2 P/F ratio, OI, and PaCO₂ at four time points in first 24 h of prone positioning. Day 1 PaO₂/FiO₂ ratio, OI, and PaCO₂. *Top:* The PaO₂/FiO₂ ratios among the four data collection points were significantly different ($p=0.006$). The PaO₂/FiO₂ ratio significantly increased ($p=0.04$) from 143 ± 10 mmHg at baseline in the supine position to 173 ± 14 mmHg after 1 h in the prone position. It continued to increase significantly ($p=0.005$) to 194 ± 15 after 19 h in the prone position. The PaO₂/FiO₂ ratio at hour 21 in the supine position (150 ± 11 mmHg) was not significantly different from that at baseline.

Middle: The OIs among the four data collection points were significantly different ($p=0.01$). The OI significantly decreased ($p=0.05$) from a baseline value in the supine position of 15.7 ± 1.7–13.6 ± 1.6 after 1 h in the prone position and continued to decrease significantly ($p=0.008$) to 10.9 ± 1.5 after 19 h in the prone position. The OI at hour 21 in the supine position (14 ± 1.9) was not significantly different from that at baseline. *Bottom:* PaCO₂ values were not significantly different among the four data collection points (From Curley et al. (2000))

was not sustained after patients returned to the supine position. Overall, studies using oxygenation as an outcome for response to prone positioning have shown variability in response and an inability to predict which patients might respond to the intervention.

It has been demonstrated in a number of clinical trials in adults with ARDS that improved oxygenation is not associated with improved clinical outcomes (ARDSnet 2000; Brower et al. 2004; Doyle et al. 1995). The only randomized, controlled trial of the prone position in pediatric

patients that evaluated relevant clinical outcomes as well as gas exchange was published in 2005 (Curley 2005). The study population included 102 patients, aged 2 weeks to 18 years, from seven pediatric intensive care units who were enrolled within 48 h of meeting criteria for ALI or ARDS. To ensure uniform co-interventions among the patients, the two groups were managed using identical ventilator protocols, extubation readiness testing, sedation protocols, and guidelines related to hemodynamics, nutrition, and skin care. Patients in the prone positioning group spent

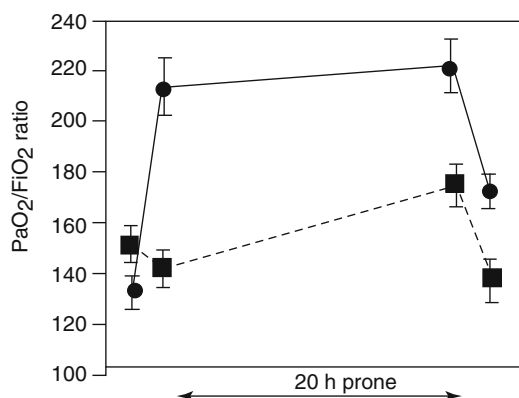


Fig. 23.3 The $\text{PaO}_2/\text{FiO}_2$ ratio was significantly different between the two subgroups ($p=0.05$) over the four data collection points ($p=0.003$) and between the two subgroups over the four data collection points ($p=0.03$). Immediate responder group (●): The $\text{PaO}_2/\text{FiO}_2$ ratio significantly increased ($p=0.003$) from a baseline value in the supine position of 134 ± 11 – 213 ± 21 mmHg after 1 h in the prone position. Significant ($p=0.02$) but not cumulative increases in oxygenation were seen after 19 h in the prone position (220 ± 25 mmHg). The $\text{PaO}_2/\text{FiO}_2$ ratio at hour 21 in the supine position (170 ± 12) was significantly better than that at baseline in the supine position ($p=0.02$). Immediate nonresponder group (■): The $\text{PaO}_2/\text{FiO}_2$ ratio did not significantly increase from a baseline value in the supine position of 152 ± 16 – 141 ± 13 mmHg after 1 h in the prone position. Significant ($p=0.02$) and cumulative increases in oxygenation were seen after 19 h in the prone position (173 ± 15 mmHg). The $\text{PaO}_2/\text{FiO}_2$ ratio at hour 21 in the supine position (135 ± 15 mmHg) was not significantly better than that at baseline in the supine position. Note that with the exception of increasing the FiO_2 to keep SpO_2 at $>85\%$, ventilator settings were held constant during the 1-h supine-to-prone and prone-to-supine repositioning (From Curley et al. (2000))

20 h/day in the prone position, for a maximum of 7 days. The primary outcome was ventilator-free days, and the secondary outcomes included mortality, time to recovery from lung injury, and organ-failure-free days. The authors did not demonstrate significant differences in either the primary outcome or any of the secondary outcome variables. The study was designed to enroll patients early in their presentation and to follow them throughout the acute phase, with patients placed prone on average of 28 h after fulfilling eligibility requirements and being treated for 79 % of the acute phase of the illness. Consistent with an earlier study on the prone position (Curley et al. 2006), this study demonstrated that 90 % of patients managed in the prone position were

categorized as responders, defined by an improvement in P/F ratio or OI. Despite a robust study design, which included early enrollment, algorithms for all relevant interventions likely to affect the primary outcome, and a high rate of compliance with all treatment protocols, the study failed to show a clinically relevant benefit of prone position in the treatment of pediatric ARDS or ALI.

A recent meta-analysis of studies on prone positioning in both adult and pediatric ARDS revealed no significant improvement in mortality (Abroug et al. 2008). A meta-analysis of adult trials also demonstrated no significant overall improvement in mortality, though there was a significantly improved mortality in patients with higher severity of illness (Alsaghir and Martin 2008). No studies have demonstrated that prone positioning in patients with ARDS improves mortality, though one recent trial has shown a trend toward improved 60-day survival in adults (Fernandez et al. 2008).

Another important consideration when evaluating pediatric studies on prone positioning is the duration of prone positioning. The timing of prone positioning ranges from a single 30-min prone maneuver in one study to other studies that place patients prone from 8 to 24 h a day (Murdoch and Storman 1994). Some studies report early improvement in hypoxemia in patients who respond to prone positioning. Relvas and colleagues performed a retrospective analysis of patients with ARDS placed in the prone position and compared the OI prior to the intervention to OI values after brief (6–10 h) and prolonged (18–24 h) periods of prone ventilation (Relvas et al. 2003). The patients placed in a prone position for a prolonged period of time demonstrated a more pronounced and stable reduction in OI than did patients placed prone for brief periods (Curley et al. 2006; Kornecki et al. 2001).

23.5 Indications and Contraindications

Because prone positioning has not been shown to have a positive impact on clinical outcomes, it should not routinely be used in the care of pediatric patients with ALI and ARDS.

Prone positioning may be used in patients with ARDS and refractory hypoxemia as a recruitment maneuver. Particularly in patients with extrapulmonary ARDS, whose lungs may be more “recruitable,” prone positioning may prove helpful. The duration of prone positioning may be limited by practical considerations that include patient size and clinical status. Patients who do not show an immediate oxygenation response may not be good candidates for continued prone positioning.

In some patients, prone positioning may not be a practical intervention. This may include patients who are unable to be positioned due to body habitus (e.g., extreme obesity or recent abdominal surgery), patients unable to tolerate prone positioning (e.g., neurologic trauma), and patients undergoing therapies that make the changes in position challenging (e.g., extracorporeal membranous oxygenation or continuous venovenous hemofiltration). Compared to adults, pediatric patients may be more safely placed in the prone position due to their size (Fineman et al. 2006).

As noted above, prone positioning is unlikely to be beneficial in a patient whose lung is not recruited. Prior to placing a child in the prone position, clinicians should evaluate the patient for lung inflation and aim to achieve optimal lung recruitment. To assess the degree of recruitment, clinicians should rely on oxygenation and on measurement of lung mechanics to evaluate the response to recruitment maneuvers at the bedside.

23.6 Complications

Before a clinician makes the decision to employ prone positioning in a child with ARDS, one must weigh the benefits of this maneuver with its potential adverse effects. The potential complications associated with prone positioning include tissue injury and nerve injury at pressure areas (Casado-Flores et al. 2002; Winfree and Kline 2005), decreased venous return and dependent edema, changes in intraocular pressure (Hunt et al. 2004), problems accessing or positioning lines and tubes, difficulty accessing patients during resuscitation (Vollman 1997), risk of disconnection of lines and

tubes, and delay in recognition of cardiorespiratory deterioration. Utilizing a well-designed algorithm along with well-trained personnel who are familiar with the maneuver can minimize the risks of these complications (Curley et al. 2006; Martin de la Torre Martin et al. 2000).

Dependent edema is a common complication of prone positioning. Many of the studies delineating complications of prone ventilation were performed in adults. In these patients, edemas of the face, eyelids, conjunctiva, lips, and tongue increase progressively after a few hours of prone positioning. Though the edema is reversible, it may be difficult to avoid, even with frequent changes in patient position (Chatte et al. 1997; Fridrich et al. 1996).

Dislodgement of invasive tubes and lines is an important potential complication of the prone positioning maneuver, though studies suggest that this complication is relatively uncommon if the position change is performed in a planned manner. In a study by Marcano and colleagues, the authors found that prone positioning of pediatric patients does result in cephalad movement of the endotracheal tube (Marcano et al. 2003). The study involved the review of 15 pairs of radiographs before and after prone positioning in 14 patients. The authors recommend placement of the tip of the endotracheal tube deeper than the level of one-third tracheal length to avoid potential cephalad movement and dislodgement. In the randomized trial summarized above involving 102 patients, none of the 51 patients placed prone were inadvertently extubated during the process of repositioning, and the rate of inadvertent extubation over the period of study was similar to that previously reported in supine children (Fineman et al. 2006). Haefner and colleagues described their institutional experience with prone positioning in patients receiving ECMO therapy (Haefner et al. 2003). In 962 position changes among 93 patients, no unplanned extubations, tube displacements, skin pressure ulcerations, or corneal abrasions were reported. Of particular importance to clinicians considering prone positioning in this patient population, the incidence of bleeding from cannula and tube insertion sites was no higher in this patient population than in other ECMO patients.

Skin breakdown and ulceration are other important concerns in patients placed in the prone position. Jolliet and colleagues reported pressure ulcers in 3 of 19 patients in their study which utilized a 12-h period of prone positioning (Jolliet et al. 1998). Willems and colleagues reported one subject that developed bilateral nipple ulcers after a 5-day period of being prone (Willems et al. 1998). In a study where head and arm position was changed every 2 h, Fridrich and colleagues reported minor skin changes but no pressure ulcers (Fridrich et al. 1996). Pediatric studies of prone positioning have reported similar potential complications. In the study by Casado-Flores and colleagues, children with ARDS were placed in the prone position and then repositioned to the supine position every 8 h for 10 days on average (Casado-Flores et al. 2002). The protocol included the application of pads and massage to pressure points. The authors reported complications of knee scarring in two patients and external ear necrosis in a single patient. In a series of 25 children managed with a protocol which utilized a prone positioning device which suspended the abdomen as well as pressure-relieving material at areas of patient contact, 24 % of the patients enrolled in the study developed stage II pressure ulcers, but none developed clinically relevant skin breakdown (Curley et al. 2006).

Corneal edema and ulcerations are serious complications that have been described in association with prone positioning. They have the potential to cause loss of vision if not discovered and treated early. Stocker and colleagues reported a case report of a patient who developed corneal ulceration that ultimately required corneal transplantation (Stocker et al. 1997).

Prone positioning may have effects on intra-abdominal pressure and may thereby affect renal function and patient hemodynamics. Hering and colleagues reported the effect that prone positioning had on intra-abdominal pressure, renal function, and cardiovascular function in mechanically ventilated adults (Hering et al. 2001). The authors reported an improvement in systemic oxygenation with no change in hemodynamic status or renal function and perfusion. Intra-abdominal pressure increased by 12–14 mmHg

in the prone patients, though no attempts were made to suspend the abdomen.

23.7 Practical Steps for Staff

In order to minimize the risk of iatrogenic injury due to prone positioning, an institutional protocol for standardization is recommended. [Appendix 23.1](#) includes the protocol for prone positioning utilized by in a previously summarized trial (Curley 2005). The protocol begins with a checklist that helps the practitioner anticipate and plan for potential problems that might arise during a turning maneuver. An important part of safely turning a patient is having adequate personnel participating in the turning. The clinician should anticipate and be ready to intervene if any changes in the patient's respiratory mechanics are detected after the position change. Prior to repositioning, a team member should check and secure all invasive lines and tubes. To prevent damage to the skin, face, and eyes, the team should use pressure-relieving positioning aides. Any new protocols should include the involvement of the pediatric physical therapist. After the actual position change, the bedside team should monitor the patient closely for pressure ulcers or corneal injury.

In patients who are maintained on high-frequency oscillatory ventilation (HFOV) in the prone position, we have noted another important safety issue. Current HFOV ventilators do not have safety alarms for detecting decreased tidal volume. Clinicians often rely on chest movement or the “wobble factor” to determine the efficacy of oscillations. A transition to the prone position can impair the amplitude of oscillations and therefore result in rapidly increasing hypercapnia. This potential side effect should be anticipated and documented with early arterial blood gases after repositioning.

23.8 The Future

As noted above, no studies to date have demonstrated that improved oxygenation decreases mortality in patients with ARDS. Future studies

should focus on the use of prone positioning in select subsets of patients with ARDS, such as those with higher severity of illness or those with extrapulmonary ARDS. In addition, studies should focus on long-term outcomes rather than short-term physiologic endpoints or short-term mortality. Indeed, studies investigating long-term outcome in adults with ARDS have revealed that they experience significant pulmonary morbidity, including persistent oxygen requirement, and non-pulmonary morbidity, including muscle fatigue, atrophy, and weakness (Herridge et al. 2003). Assessments of long-term outcome of therapeutic interventions in ARDS should monitor, quantify, and evaluate the effect on functional outcomes, as well as mortality.

23.9 Summary and Conclusion

Prone positioning has been well described as a maneuver to improve oxygenation in patients with ARDS and ALI. Through a variety of physiologic mechanisms, most importantly an improvement in lung recruitment and V/Q matching, application of mechanical ventilation to patients in the prone position may have an immediate and prolonged effect on oxygenation. Though no

studies have shown that prone positioning has a significant effect on clinical outcomes, it is a safe maneuver that may be employed in select populations of children with ARDS. However, in the absence of proven improvements in clinical outcomes, prone positioning should not be a part of the routine management of these patients.

Essentials to Remember

- Prone positioning improves oxygenation in diseased lungs through improvement in lung recruitment, better matching of ventilation and perfusion, and changes in chest wall compliance.
- Clinical studies evaluating the use of prone positioning for ARDS and ALI in pediatric patients, including a recent multicenter randomized controlled trial, have failed to show significant improvements in clinical outcomes.
- With attention to safe turning and to interventions to minimize possible complications, prone positioning may be safely employed in children with ARDS or ALI, but should not be routinely used in this patient population.

Appendix 23.1: Prone Positioning Check Sheet

<i>Preparation (prior to getting help into room)</i>	
☐	Create cushions using egg crate material (head, chest, pelvic, distal femoral, and lower limb).
☐	Insert transpyloric feed tube and check placement.
☐	Check ETT on CXR—tip should be in the lower 1/3 of the thoracic trachea.
☐	Assess the security of the ETT, vascular lines, and SpO ₂ probe and reinforce as necessary. Retape the ETT to the upper lip on the side of the mouth that will end in the “up” position. Place a protective layer of plastic tape over the white adhesive tape holding the ETT.
☐	If cuffed ETT/trach, inflate cuff using minimal leak technique (cuff pressure under 25 mmHg).
☐	Protect eyes if chemically paralyzed and/or open (cleanse, lubricate, cover with plastic wrap).
☐	If HFOV, apply plastic film dressing over anterior bony prominences to avoid friction injury.
☐	Move EKG electrodes to the lateral aspects of the upper arms and hips.
☐	Remove clothing surrounding thorax and abdomen.
☐	Coil then secure bladder catheter to inner thigh.
☐	Suction the patient’s oropharynx. (If ETT suctioned, postpone turn until unit patient returned to pre-suctioning ventilator settings.)
☐	Temporarily cap nonessential vascular lines and the patient’s NGT/JT.
☐	<i>Final Check</i> —Review the start and end point of all that is left attached to the patient. Arrange the remaining vascular lines and Foley catheter tubing to prevent excessive tension.
☐	Premedicate with comfort medications at the discretion of the bedside nurse.
<i>Turning</i>	
☐	Call for RT and at least one other nurse.
☐	Preplan responsibility: RT, head/ETT; Nurse 1, chest/arms; Nurse 2, hips/legs.
☐	Review technique: <i>Infants/toddlers:</i> Levitate—levitate up, turn 45°, pause/reassess, turn prone, and levitate up to place cushions under the subject. <i>School aged/adolescents:</i> Mummy—using all bed linens, slide patient to the edge of the bed away from the ventilator and place new draw sheet over patient; position chest and pelvic cushions over draw sheet; place full sheet over entire patient; create a mummy effect by tucking the edges of the full sheet under patient; turn patient 45° toward ventilator, pause/reassess, and position patient prone on new linen and cushions/ remove old linen.
☐	Keep head in alignment with body, avoid hyperextension, keep arms next to torso, and point toes of the upper leg in the direction of turn.
☐	Turn toward the ventilator without disconnecting. (FiO ₂ may be manipulated to maintain target SpO ₂ . All other ventilator settings remain constant until 1-h post turn ABG obtained.)
☐	Talk the patient through the turn.
<i>Immediately after the turn</i>	
☐	Reassess the security and patency of all tubes/lines.
☐	Reassess SpO ₂ , blood pressure, cardiac rhythm, and breath sounds.
☐	Reassess ETT/trach leak (may adjust cuff volume, head position, delivered V _t to assure adequate ventilation).
☐	Uncap/reattach capped off lines/NGT/NJT.
☐	Position the patient: Turn head to side and cushion head and ear with pressure-relieving material. Place an absorbent diaper under the patient’s mouth. Avoid excessive flexion/extension of the spine; cushion the upper chest and pelvis—check that the abdomen is unrestrained. In males, check that the penis and scrotum are unrestrained. In adolescent females, check that the nipples are away from chest rolls. Flex arms up. Position knees and feet off bed using a roll under the distal femur and lower leg. Check that everything attached to the patient is not pressing against their skin (ETT balloon port) and that the patient’s skin is not pinched in any way (periumbilical area).

Return to supine

- ☐ Precautions and techniques described above apply.
- ☐ Consider performing the patient's daily suctioning procedure.
- ☐ Turn patients away from the ventilator without disconnecting.
- ☐ Position the patient:
 - Cushion head using pressure-relieving materials (pillow, jell pillow, or Spenco pad).
 - Elevate the patient's heels off the bed using an appropriate size pillow.

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Respiratory Physiotherapy and Endotracheal Suctioning During Mechanical Ventilation

24

Brenda M. Morrow and Andrew C. Argent

Educational Aims

- Review the effects of chest physiotherapy and endotracheal suctioning clinically and on lung mechanics.
- Discuss the potential indications and precautions to suctioning and chest physiotherapy.
- Discuss the various intervention modalities and techniques.
- Consider the impact of chest physiotherapy and suctioning for specific paediatric conditions.
- Present an evidence-based clinical practice guideline for chest physiotherapy and suctioning techniques and their application in ventilated infants and children.

Despite widespread practice, very little high-level evidence dealing with paediatric chest physiotherapy (CPT) and endotracheal (ET) suctioning exists. Studies of mechanically ventilated paediatric, neonatal, and adult patients have shown that both interventions may cause a range of potentially serious complications.

There is still no clear evidence that CPT and ET suctioning improve respiratory mechanics with most studies pointing instead to their detrimental effects. CPT and ET suctioning should, therefore, not be routine but performed only when obstructive secretions are present and impacting on lung mechanics and/or gaseous exchange.

Different treatment modalities and techniques are discussed with evidence-based recommendations for clinical practice.

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24.1 Introduction

Endotracheal suctioning (ET) and chest physiotherapy (CPT) are part of the accepted care of intubated children in many paediatric intensive care units (PICUs) globally in spite of a limited evidence base (Krause and Hoehn 2000; Stiller 2000), largely because of the risks of endotracheal tube (ETT) obstruction.

Intubated patients are unable to clear secretions effectively as glottic closure is compromised, limiting the pressures and velocity of airflow that can be generated for an effective cough, and normal mucociliary function may be

impaired (Bailey et al. 1988). Inadequately humidified inspired gas and the ETT itself may cause irritation of the airways and increased secretion production (Fisher et al. 1990). In addition, many children with respiratory tract infections (RTI) have increased sputum volume and altered sputum rheology which further impedes secretion clearance. Therefore, all infants and children with an artificial airway require ET suctioning and some may benefit from CPT, to remove secretions and prevent airway obstruction (Guglielminotti et al. 2000; Young 1995).

This chapter presents a review of ET suctioning and respiratory physiotherapy practice for ventilated children and provides evidence-based clinical recommendations.

24.2 Respiratory Physiotherapy

The main role of CPT in paediatric respiratory disease is to assist in the removal of obstructive tracheobronchial secretions, thereby aiming to reduce airway resistance, reduce the work of breathing, improve gas exchange, facilitate early weaning from the ventilator, prevent and resolve respiratory complications, re-expand collapsed lobes, and hasten recovery (Main et al. 2004; Ntoumenopoulos et al. 2002; Wallis and Prasad 1999; Ciesla 1996; Oberwaldner 2000). The precise role of the physiotherapist in different intensive care settings varies according to the country of location, local tradition, staffing levels, training, and expertise (Stiller 2000).

The most common modalities used by physiotherapists for ventilated paediatric patients are gravity-assisted positioning or postural drainage, mobilisation, percussion and vibration (manual techniques), and ET suctioning (Stiller 2000). Manual hyperinflation is frequently used in adult ICUs (Stiller 2000) and less commonly in PICUs.

Although there is some suggestion that CPT is useful in certain circumstances and disease conditions, it may be useless or harmful in other situations (Wallis and Prasad 1999). In the critically ill child, any potential benefits of CPT must be very carefully weighed up against the potential complications before implementing such therapy.

24.2.1 Effects of Chest Physiotherapy

Adult studies have examined the effects of multi-modality CPT on pulmonary function in ventilated patients, with variable results. Short-term improvements in lung compliance, arterial blood gases, and intrapulmonary shunt have been reported, whilst other studies have shown no benefit of CPT in terms of pulmonary function. Significant cardiovascular, metabolic, and neurological sequelae have been reported, including increases in heart rate, blood pressure, cardiac output, oxygen consumption, carbon dioxide production, and intracranial pressure. CPT was shown to cause the most pronounced variation in vital signs when compared to any other routine ICU interventions (Weissman et al. 1984). A systematic review on the topic noted that virtually all of the available studies were observational without a control group and treatments were not standardised, limiting validity (Stiller 2000).

Unfortunately, the evidence base for CPT in PICU is even more limited, with few studies having been performed on infants and children. Those that exist are limited methodologically by design and lack of intervention standardisation. Many studies suggest that CPT may do more harm than good (Krause and Hoehn 2000; Wallis and Prasad 1999; Weissman et al. 1984; Chalumeau et al. 2002; Chaneliere et al. 2006; Harding et al. 1998; Button et al. 1997, 2004; Reines et al. 1982; Zidulka et al. 1989). As for adults, CPT and suctioning of ventilated children may affect the respiratory system, cardiovascular system, central nervous system, and metabolic demand.

In a randomised crossover trial comparing ET suctioning alone with CPT and suctioning (Main et al. 2004; Main and Stocks 2004), the CPT group showed better tidal volume, respiratory compliance, and alveolar dead space than the suction group; however, this was not translated into an improvement in blood gases. There was a greater drop in airway resistance in the CPT group, suggesting better secretion clearance than suction alone. However, approximately 30 % of subjects in both groups deteriorated following the study intervention, and the authors could not identify reasons for response or lack thereof to

therapy. This study was limited in that, in an attempt to simulate the clinical situation, there was no intervention standardisation (Main et al. 2004; Main and Stocks 2004).

Numerous complications have been attributed to CPT, although the contribution of ET suctioning to these is unclear: hypoxia, increased metabolic demand and oxygen consumption, cardiac arrhythmias, changes in blood pressure, raised intracranial pressure and decreased cerebral oxygenation, gastro-oesophageal reflux, pneumothoraces, rib fractures and periosteal reactions, atelectasis, and death (Wallis and Prasad 1999; Chalumeau et al. 2002; Chaneliere et al. 2006; Harding et al. 1998; Button et al. 1997; Reines et al. 1982; Zidulka et al. 1989; Fox et al. 1978; Gray et al. 1999; Argent and Morrow 2004; Vandenplas et al. 1991).

The effect of CPT on patient outcome has only been assessed in one paediatric randomised controlled trial which showed an increased length of hospital stay in patients who received CPT following cardiac surgery, compared to the control group (Reines et al. 1982).

24.2.2 Indications for Chest Physiotherapy

In mechanically ventilated children, CPT cannot be regarded as a standard treatment modality. CPT must be considered as the most stimulating and disturbing intensive care procedure in mechanically ventilated patients and should not be administered in children with low cardiopulmonary reserve attributable to increased oxygen consumption and increases in intracranial pressure. (Krause and Hoehn 2000)

Considering that the main aim of CPT is to reduce or eliminate the mechanical consequences of obstructive secretions, one should consider the childhood diseases which are characterised by either excessive airway secretions or an inability to clear those secretions as potentially benefiting from CPT (Schechter 2007).

For some physiotherapists, just the presence of an ETT is considered sufficient indication for CPT, considering the potential effects on secretion retention. Ventilated children are at risk of ventilator-induced lung injury, ventilator-associated

pneumonia (VAP), oxygen toxicity, hyperinflation, positional atelectasis and/or consolidation, impaired mucociliary clearance, and decreased functional residual capacity due to loss of laryngeal braking (Schechter 2007). The ETT, combined with inadequate humidification of ventilator gases, may lead to an increased amount and tenacity of pulmonary secretions which could lead to obstruction, infection, atelectasis, and ultimately chronic lung disease (Clini and Ambrosino 2005). However, the evidence relating to the benefits of 'prophylactic' CPT for intubated children is sparse.

CPT does not appear to prevent postextubation atelectasis in neonates, based on a systematic review of three small randomised controlled trials (Flenady and Gray 2002). A randomised controlled trial of paediatric patients following surgery for congenital cardiac defects showed that children receiving CPT developed atelectasis significantly more frequently and more severely than the control group (68 % of treated group vs. 32 % untreated developed atelectasis). The inverted position used may have caused hypoventilation; the compression caused by the manual techniques may have led to airway collapse; and the pain induced by CPT could have led to splinting and a reduction in functional residual capacity. This study, despite some limitations, showed that there is no benefit from the use of routine CPT in postoperative paediatric cardiac surgical patients and that CPT may, in fact, be harmful. A systematic review of 35 adult studies also concluded that CPT was not justified routinely after abdominal surgery (Pasquina et al. 2006).

In a prospective randomised controlled trial of 180 ventilated adults, CPT was associated with prolonged ventilator dependence (Templeton and Palazzo 2007). This would seem to predispose to VAP which is directly related to length of time being mechanically ventilated. Conversely, however, another prospective controlled systematic allocation study of 60 adults showed that CPT was independently associated with a reduction in VAP (Ntoumenopoulos et al. 2002). A more recent randomised controlled trial showed that CPT did not prevent, or hasten recovery from, VAP in adult patients with brain injury (Patman et al. 2009). These studies require confirmation in further randomised controlled trials.

Considering the lack of evidence supporting the use of prophylactic CPT in ventilated infants and children, as well as the potential complications, it is suggested that respiratory management of ventilated children focuses on good general nursing and ventilatory management, including analgesia, regular changes in position and early mobilisation, lung protective ventilatory strategies, minimal effective inhaled oxygen levels, adequate humidification, and impeccable hygiene and infection control practices. Physiotherapists should engage in the above holistic care practices, but formal, 'conventional' CPT is not indicated routinely for ventilated children (Schechter 2007).

A comprehensive review of the literature concluded that the only condition for which there was reasonable evidence supporting the use of CPT is that of cystic fibrosis (Schechter 2007). Despite a lack of robust scientific evidence, there is consensus that CPT is of probable benefit for the treatment of atelectasis caused by mucus plugging (Schechter 2007; Peroni and Boner 2000; Bilan et al. 2009; Galvis et al. 1994) (Fig. 24.1) and for the management of paediatric neuromuscular disease (Schechter 2007). There is no way that CPT can improve atelectasis, unless it is by the removal of mucus plugs (Branson 2007), so patients with atelectasis caused by extrinsic bronchial compression should

not receive CPT. CPT has been shown to be of minimal to no benefit (and may in fact be harmful) in acute asthma (Asher et al. 1990), bronchiolitis (Webb et al. 1985; Nicholas et al. 1999; Perrotta et al. 2007), respiratory failure without atelectasis (Schechter 2007), and undrained pleural collections. Randomised controlled trials of adults hospitalised with primary pneumonia have not found any benefit of CPT (Britton et al. 1985; Graham and Bradley 1978).

It is important to note that the 'indications or contraindications for or against chest physiotherapy should never be formulated on the basis of diagnostic entities but should rather stem from a detailed analysis of the prevailing individual pathophysiology' (Oberwaldner 2000). Therefore, when deciding on whether or not CPT may be beneficial, consider the following: if there is an excessive amount and/or retention of secretions, and if so if this is impacting on lung mechanics and/or gaseous exchange, or if there is the potential for further complications, and if there is lung or lobar collapse and whether this is due to intrinsic mucus plugging or extrinsic compression.

Considering the known complications of CPT, relative contraindications and precautions to CPT include severely ill, unstable children; pulmonary haemorrhage (spontaneous or after surfactant treatment); pulmonary oedema; coagulation

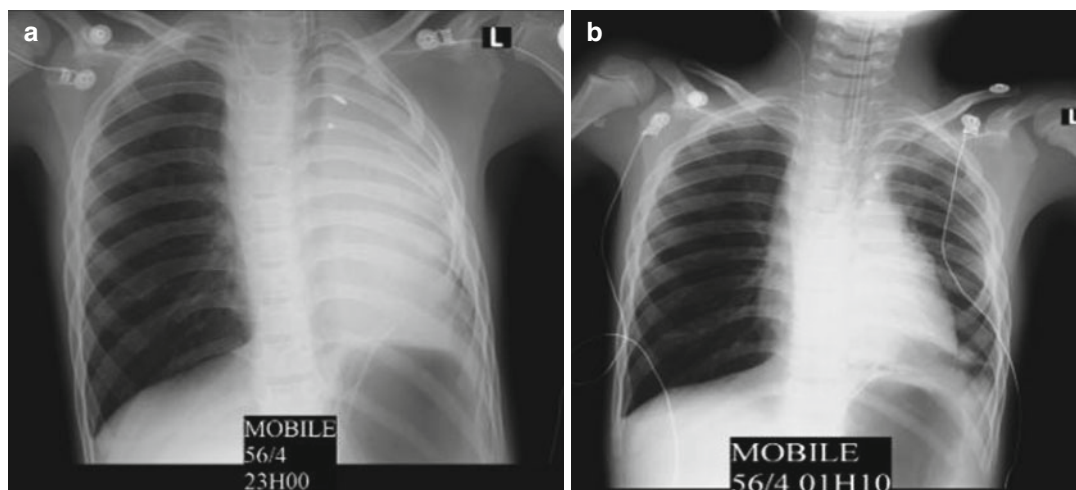


Fig. 24.1 Left lung collapse due to mucus plugging before (a) and after (b) chest physiotherapy

defects; raised or unstable intracranial pressure; pulmonary hypertension and/or a history of hypertensive crises; and very premature or small for gestational age infants. However, in certain cases CPT may be beneficial even in children presenting with one or more of the above conditions. For example, a child with raised intracranial pressure and acute lung collapse may benefit from CPT if the lung pathology is resulting in hypoxia and hypercapnia which could lead to further increases in intracranial pressure. The physiotherapist working in PICU must be aware of intersystem dynamics and take appropriate precautions if treatment is deemed necessary.

24.2.3 Modalities

...in the case of young children with respiratory disease, we have few effective therapies, and when [you think] your only tool is a hammer, everything starts to look like a nail. ... patients have respiratory difficulties from a variety of causes, but we have one hammer, so we try it on everybody. (Schechter 2007)

A number of CPT modalities are used when treating the critically ill child, but few of these have been rigorously tested scientifically.

24.2.3.1 Positioning

Positioning uses gravity to move secretions from peripheral to proximal airways thereby enhancing mucociliary clearance (postural drainage), increasing lung volumes, reducing the work of breathing, minimising the work of the heart, and optimising ventilation/perfusion ratios (Stiller 2000; Cline and Ambrosino 2005). Historically a number of postural drainage (PD) positions were advocated, with no supporting objective evidence, including inverted or head-down positions. However, head-down positioning has been shown to increase systemic blood pressure with the potential for intraventricular haemorrhage in neonates (Crane et al. 1978), increase gastro-oesophageal reflux (Vandenplas et al. 1991; Button et al. 2003) and intracranial pressure (Emery and Peabody 1983), place the diaphragm at mechanical disadvantage (Vivian-Beresford

et al. 1987), and may increase venous return thereby increasing the work of the heart.

Despite no proven effect on patient outcome (Curley et al. 2005), turning patients from the supine to prone position has been shown to dramatically improve oxygenation in mechanically ventilated adults and children with acute lung injury (Casado-Flores et al. 2002; Dupont et al. 2000; Jolliet et al. 1998; Kornecki et al. 2001; Pelosi et al. 1998). It has been suggested that prone positioning recruits atelectatic dorsal regions of the lung, limits anterior chest wall movement, and reduces the effects of abdominal pressure on the thoracic cavity, thereby promoting more uniform alveolar ventilation (Matthews and Noviski 2001); perfusion is redistributed away from the previously dependent lung region (Pelosi et al. 1998); and there may be improved ventilation/perfusion matching with a reduction in intrapulmonary shunt (Marraro 2003).

The PD positions advocated for clearing secretions from specific lobes or segments have never been objectively shown to be effective, and the upright position in comparison has been shown to increase end-expiratory lung volume, optimise oxygenation, and prevent ventilator-associated pneumonia (Drakulovic et al. 1999; Stark et al. 1984; Dellagrammaticas et al. 1991). Therefore, in PICU practice the inverted position should never be used. Other positions such as side lying, upright sitting, and prone should rather be used according to the indication, preferably with the head of the bed raised (Fig. 24.2).

24.2.3.2 Mobilisation

Teach us to live that we may dread
Unnecessary time in bed.
Get people up and we may save
Our patients from an early grave. (Asher 1947)

Mobilisation techniques that can be used for intubated, ventilated patients, depending on the patients' stability, age, developmental level, and general condition, include active limb exercises, rolling or turning in bed, sitting in or out of bed on a chair, standing, and walking (with or without assistance) (Stiller 2000) (Fig. 24.3a, b). Mobilising patients out of bed is commonly practised in an

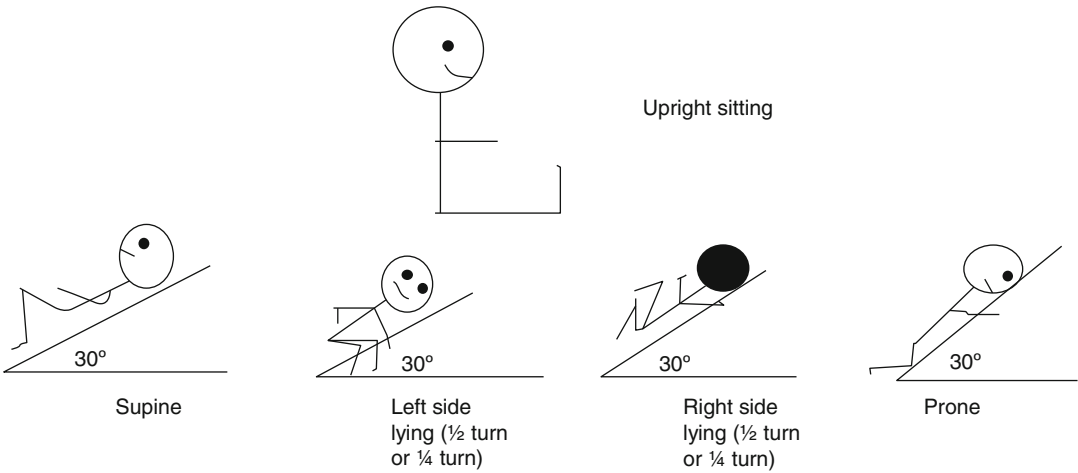


Fig. 24.2 Modified postural drainage positions for paediatric practice

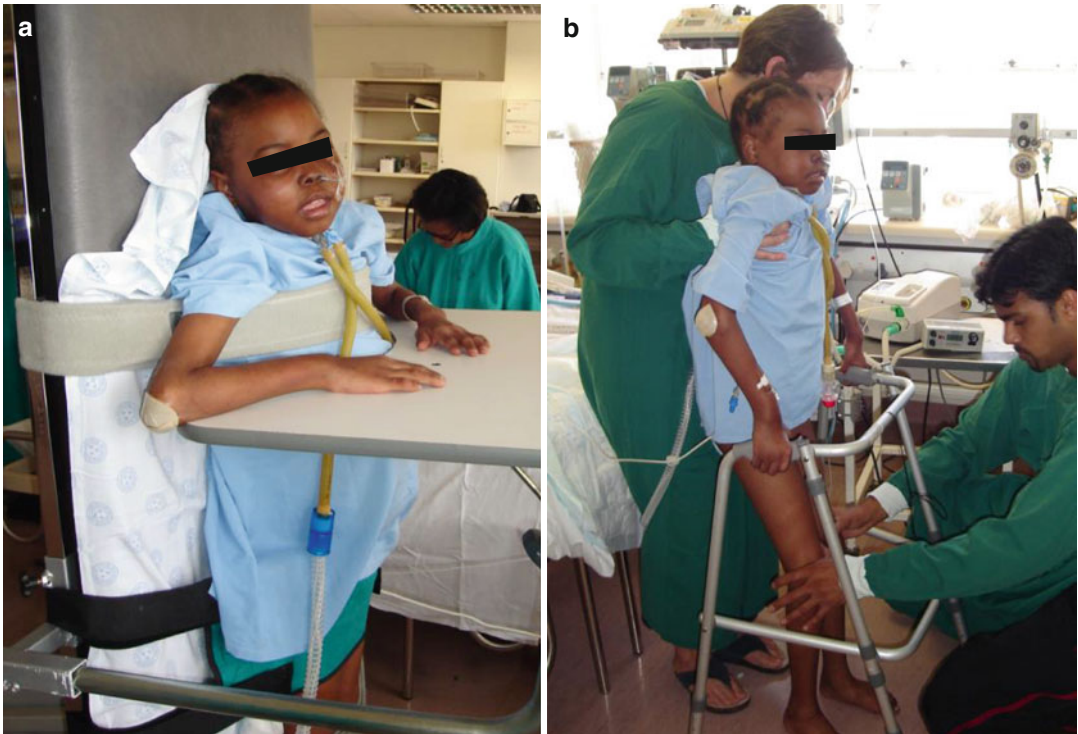


Fig. 24.3 A 10-year-old girl with following prolonged PICU stay after posttransplant complications (Photograph with parental and patient consent). **(a)** Mobilised to stand-

ing on tilt table (fully ventilated). **(b)** Assisted mobilisation using walking frame (on BiPAP ventilation)

attempt to prevent atelectasis, stimulate a cough, and improve circulation, but there is little scientific evidence supporting the practice (Stiller 2000; Branson 2007). The aims of mobilisation are numerous, including improving thoracic mobility;

increasing lung volumes (Zafiropoulos et al. 2004); assisting secretion clearance; improving exercise tolerance, muscle strength, and cardiovascular fitness (Stiller 2000); preventing postural deformities; improving bone ossification; benefiting bladder and

bowel function; and psychological benefits (Bailey et al. 2007). In adults, mobilisation has been shown to be safe and feasible in the early stage of ICU admission (Bailey et al. 2007). This has not been studied in the paediatric population.

24.2.3.3 Chest Manipulations

Percussion and vibration are techniques which are widely used to assist with removal of secretions from the lungs. They may be performed manually or with mechanical devices. It is thought that by applying chest manipulations to the chest wall, mechanical energy is transmitted into the airways where it liquefies thixotropic pulmonary secretions which can then be cleared by positioning, cough, or suctioning (Stiller 2000; McCarren et al. 2006b).

Manual vibration is a combination of compression and oscillation applied to the chest wall (McCarren et al. 2006a, b). Vibration has been shown to increase the expiratory flow rate via increased intrapleural pressure in a small randomised within-subject study of healthy adults (McCarren et al. 2006a).

Manual percussion is applied to the chest wall by means of a cupped hand or 'tenting' fingers (Fig. 24.4), clapping the chest wall overlying the area of pathology (Stiller 2000). Percussion has been associated with cardiac arrhythmia and a

drop in pulmonary compliance in critically ill adults (Stiller 2000).

Both percussion and vibration have been shown to cause or exacerbate bronchospasm (Kirilloff et al. 1985), and in an animal study the application of manual techniques was associated with the development of atelectasis (Zidulka et al. 1989). At present, the use of percussion or any external vibration method is unfounded and unsupported by scientific evidence (Stiller 2000; Branson 2007; Kirilloff et al. 1985).

24.2.3.4 Manual Hyperinflation

Physiotherapists working in adult intensive care units often use manual hyperinflation techniques in conjunction with other manipulations in order to expand the lung and loosen secretions (Patman et al. 2000; McCarren and Chow 1996). These manoeuvres are usually repeated deep manual inflations reaching a predetermined set pressure or volume with a brief inspiratory hold, followed by a quick release of the bag to enhance expiratory flow (Stiller 2000). Manual hyperinflation aims to prevent lung collapse, re-expand atelectasis, improve oxygenation and compliance, and enhance secretion clearance (Stiller 2000). It is of great concern that manual hyperinflation, and manual ventilation generally, is usually performed by delivering 100 % cold, dry oxygen, by means



Fig. 24.4 Percussion using the 'tenting' technique in a 3-week-old infant with aspiration pneumonia and right upper lobe collapse (Photograph with parental consent)

of devices which provide variable (often unmeasured) pressures and unknown tidal volumes, often without PEEP (O'Donnell et al. 2003).

Studies reporting the efficacy and safety of manual hyperinflation in adults have been conflicting, with some reporting improvements in atelectasis, lung compliance, and gas exchange (Stiller 2000; Patman et al. 2000; Choi and Jones 2005; Stiller et al. 1990), whilst others have found no change (Stiller 2000; Barker and Adams 2002). Other adult studies have reported increased intracranial pressure and significant cardiovascular complications (Stiller 2000). There is always the risk of overdistension of normal alveoli and barotrauma during manual hyperinflation (Stiller 2000; Branson 2007), and therefore great care should be taken when applying adult hyperinflation studies to paediatric practice.

In infants and children, performing hyperinflation manoeuvres may be especially dangerous due to the increased risk of baro- or volutrauma. The only study investigating manual hyperinflation in ventilated paediatric patients incorporated this technique into a saline-lavage-simulated cough technique, which was effective in improving lung volume in 48 of 57 infants with atelectasis not responsive to conventional CPT (Galvis et al. 1994).

It must be remembered that peak inspiratory pressure (PIP) is a proxy for inspired tidal volume. Even if the PIP is measured and controlled, one cannot directly extrapolate the tidal volume as this depends on a number of variables, particularly respiratory compliance (which changes even as the lungs expand) (O'Donnell et al. 2003). The role of 'volutrauma' in lung injury is well described, and limiting inspired tidal volume is an important component of lung protective ventilation (Dreyfuss and Saumon 1998; Brochard et al. 1998; Carpenter 2004). If the tidal volume is too large, it will contribute to lung damage regardless of the pressure applied, particularly with low lung compliance and immature, fragile lungs (O'Donnell et al. 2003). Considering the lack of evidence supporting efficacy of manual hyperventilation in infants and children, and the likely associated hazards, this practice cannot be considered an acceptable component of standard CPT in PICU practice.

24.3 Endotracheal Suctioning

Recommendations and clinical guidelines for ET suctioning have been made (Young 1995; Boothroyd et al. 1996; Branson et al. 1993; Runton 1992; Morrow and Argent 2008; Hodge 1991; Young 1984), but few of these have been objectively shown to be appropriate or safe. Surveys conducted in clinical settings suggest that suction practice guidelines and protocols vary widely and are not, in general, based on sound evidence (Tolles and Stone 1990; Copnell and Fergusson 1995). Consequently, ET suctioning practices vary widely among critical care practitioners (Kelleher and Andrews 2008).

24.3.1 Adverse Clinical Effects

The not-infrequent occurrence of cyanosis during endotracheal suctioning and an occasional death attributable to the procedure have prompted studies on the subject. (Boutros 1970)

Although considered necessary to prevent airway obstruction from accumulation of secretions, it is recognised that severe adverse events may result from suctioning: respiratory complications include hypoxia (Kerem et al. 1990; Singh et al. 1991), pneumothorax (Loubser et al. 1989; Anderson and Chandra 1976), mucosal trauma (Bailey et al. 1988; Loubser et al. 1989; Kuzenski 1978; Nagaraj et al. 1980), atelectasis (Boothroyd et al. 1996; Choong et al. 2003; Morrow et al. 2006), and loss of ciliary function (Bailey et al. 1988). Atelectasis has been attributed to the aspiration of intrapulmonic gas (Ehrhart et al. 1981), mucosal oedema (Boothroyd et al. 1996), or bronchial obstruction as a result of mucosal trauma (Nagaraj et al. 1980).

Cardiovascular complications of ET suctioning include bradycardia (Hoellering et al. 2008; Kohlhauser et al. 2000; Simbruner et al. 1981; Zmora and Merritt 1980; Cabal et al. 1979) and other arrhythmias (Simbruner et al. 1981) and increases in systemic blood pressure (Simbruner et al. 1981; Fanconi and Duc 1987). Raised intracranial pressure has been reported to occur with endotracheal suctioning (Tume and Jinks 2008; Kerr et al. 1997; Singh et al. 1991). Opiates and

neuromuscular blockade have been shown to suppress ET-suction-induced coughing in adults, thereby minimising associated increases in intracranial pressure (Kerr et al. 1998).

ET suctioning has been implicated in nosocomial bacteraemia, attributed to the introduction of pathogens by the suction catheter (Bailey et al. 1988). Endotracheal suctioning has also been shown to be painful in neonates (Evans et al. 1997; Cignacco et al. 2008) and in adults (Puntillo 1994; Payen et al. 2001). The discomfort caused by suctioning is frequently recalled upon discharge from the adult ICU (Van de Leur et al. 2003).

Neonatal studies investigating the use of intermittent, pre-suction analgesia have had conflicting results (Pokela 1994; Cignacco et al. 2008). Considering that ET suctioning cannot and should not be scheduled, it is not appropriate to recommend intermittent analgesia for ET suction-induced pain control. Therefore, regular or continuous analgesia is recommended (Morrow and Argent 2008). Non-pharmacological pain reduction strategies such as facilitated tucking and sucrose and nonnutritive sucking are promising but require further investigation (Leslie and Marlow 2006; Cignacco et al. 2007; Helder and Latour 2008).

Some of the complications of suctioning may be due to vagal nerve stimulation (Zmora and Merritt 1980), coughing, or catheter trauma (Bailey et al. 1988; Hodge 1991; Anderson and Chandra 1976), and others may be directly related to the physical effects of suctioning on the lungs (Morrow et al. 2006; Ehrhart et al. 1981; Maggiore et al. 2003; Rosen and Hillard 1962; Hippenbecker and Guthrie 1981; Brandstater and Muallem 1969; Morrow et al. 2004; Lu et al. 2000).

The effect of different ET suctioning techniques on patient outcome, length of PICU and hospital stay, and patient mortality and morbidity is currently not known, and this requires further investigation.

24.3.2 Precautions and Contraindications

Considering that all intubated and ventilated patients may require ET suctioning in order to maintain a patent airway (Fig. 24.5), there can be no absolute contraindications to the procedure (Branson et al. 1993).



Fig. 24.5 Open-endotracheal suctioning of an infant with tracheo-oesophageal fistula and pneumonia (Photograph with parental consent)

Special care should be taken with patients who have raised intracranial pressure, as this can be exacerbated by ET suctioning and coughing (Fanconi and Duc 1987; Kerr et al. 1997; Durand et al. 1989) as can pulmonary hypertension. Patients with pulmonary oedema and pulmonary haemorrhage should only be suctioned when absolutely necessary (Pang et al. 1998; Demers 1982).

All patients should be continually monitored to assess clinical and physiological changes in response to ET suctioning.

24.3.3 Effects of ET Suctioning on Lung Mechanics

Many reported complications of ET suctioning are due to the exposure of negative pressure to the tracheobronchial tree (Kiraly et al. 2008). Lung model studies have shown that the negative tracheal or thoracic pressure induced during ET suctioning is directly proportional to the suction pressure applied and is further determined by the relationship between catheter and ETT size (Morrow et al. 2004; Kiraly et al. 2008; Copnell et al. 2009). This has also been shown to apply in clinical practice with studies of lung mechanics during ET suctioning in paediatric patients (Morrow et al. 2006, 2007; Copnell et al. 2007).

Main et al. (2004) found that, overall, there were no significant changes in tidal volume or respiratory system compliance after ET suctioning in 100 paediatric patients with variable lung disease. It was noted, however, that individual responses varied with some patients showing a marked improvement, whilst others deteriorated (Main et al. 2004).

In an observational study prospectively investigating the effects of a standardised suctioning procedure in 78 ventilated paediatric patients, Morrow et al. (2006) showed that ET suctioning reproducibly resulted in a decrease in dynamic compliance and tidal volume, attributable to a loss of lung volume, which increased to pre-suction levels again within 10 min of being reconnected to the ventilator. This recurrent derecruitment and subsequent rerecruitment on

reconnection to the ventilator may exacerbate lung injury (Maggiore et al. 2003; Taskar et al. 1997; Suh et al. 2002). Choong et al. (2003) also showed that ET suctioning resulted in loss of lung volume in 14 paediatric patients receiving conventional ventilation.

Theoretically, removal of secretions from the airways should reduce airway resistance (Fox et al. 1978), but this has not been clinically demonstrated. The reduction in resistance caused by clearing the large airways could be negated if suctioning-induced volume loss occurred, with an associated increase in airway resistance. An increase in airway resistance as a result of transient bronchoconstriction following ET suctioning has also been described (Guglielminotti et al. 1998). 'Routine' suctioning, performed in the absence of secretions, would not be expected to drop airway resistance, as has been demonstrated clinically (Morrow et al. 2006; Main et al. 2004).

There is still no clear evidence that ET suctioning improves respiratory mechanics (Guglielminotti et al. 1998). Conversely, most evidence points to the detrimental effects of ET suctioning on lung mechanics. However, many available studies are limited by small sample sizes, patient heterogeneity, lack of intervention standardisation, and the absence of a suitable control group. Although in most studies the overall effect was found to be negative or of no benefit, individual patients did appear to improve their lung mechanics.

24.3.4 Frequency of ET Suctioning

It is generally accepted that suctioning should not be performed routinely but rather as indicated following a thorough clinical assessment (Branson 2007; Day et al. 2002). Observational studies of clinical practice have suggested that the identification of the need for ET suctioning is complex, involving changes in both clinical signs and patient behaviour (Thomas and Fothergill-Bourbonnais 2005).

Guidelines based on expert consensus have suggested that clinical indications for suctioning should include audible or visible secretions in the

ETT or coarse breath sounds on auscultation, coughing, increased work of breathing, arterial desaturation and/or bradycardia as a result of secretions, decreased tidal volume during pressure-controlled ventilation, the need for a tracheal aspirate culture (Guglielminotti et al. 2000; Branson et al. 1993; Branson 2007), and following CPT in order to clear mobilised secretions. If ventilators are equipped with flow-volume loop displays, changes in graphics (Branson et al. 1993) or a saw-toothed pattern may indicate the presence of secretions in the ETT. Patients receiving high-frequency oscillatory ventilation should be observed with regard to the amount of chest wall oscillation – if this changes it may indicate the presence of secretions.

Many of these indications are very subjective, and closer monitoring of, for example, transcutaneous $p\text{CO}_2$ levels may provide a more objective indication for suctioning. This requires investigation.

24.3.5 Open- Versus Closed-System ET Suctioning

As with electric hand-dryers public acceptance does not always mean demonstrable efficacy. (Lindgren 2007)

Commonly used suctioning systems are open-ET suctioning (OES) and closed-system suctioning (CSS). OES involves first disconnecting the patient from the ventilator and then suctioning the ETT before reconnecting the patient to the ventilator circuit. CSS is performed through an adaptor inserted at the ETT-ventilator circuitry interface. The catheter is encased in a plastic sleeve on insertion, providing a seal that maintains a closed system (Taggart et al. 1988), allowing ventilation to continue during the suctioning procedure.

Initial studies suggested that use of CSS may prevent ET suctioning-induced hypoxia and decreases in lung volume in paediatric (Choong et al. 2003) and adult (Taggart et al. 1988) patients. However, animal and clinical studies have shown no advantage of CSS in terms of lung volume protection (Copnell et al. 2009;

Tingay et al. 2010; Hoellering et al. 2008; Heinze et al. 2008) (Table 24.1).

The drawbacks of CSS include the risk of producing high negative pressures (Stenqvist et al. 2001) if the amount of air suctioned exceeds the gas flow delivered to the patient by the ventilator, reduced efficiency in clearing secretions from the airways (Copnell et al. 2007; Lindgren et al. 2004), and the high financial cost of the system which has to be replaced regularly in order to avoid microbial lower respiratory tract colonisation (Freitag et al. 2003; Meyer et al. 2009). Practically, there is also a risk of not withdrawing the catheter completely after the suctioning event, thus partially occluding the ETT and increasing airway resistance.

It has been suggested that CSS could reduce the risk of VAP by eliminating environmental contamination of the catheter before introduction into the ETT (Cobley et al. 1991). However, this has not been shown in a number of clinical studies (Table 24.1).

24.3.6 Preoxygenation

A meta-analysis of 15 adult studies showed that the occurrence rate of hypoxia was 32 % lower when preoxygenation was applied before suctioning than if it was not applied (Oh and Seo 2003).

Kerem et al. (1990) examined ways of preventing hypoxia during ET suctioning in a prospective crossover trial of 25 haemodynamically stable paediatric patients. Patients underwent one of four suctioning approaches: preoxygenation, hyperinflation pre-suction, hyperinflation post-suction, and a control with no treatment. The significant fall in SaO_2 and PaO_2 occurring as a result of suctioning was completely prevented by delivering 100 % inspired O_2 for 1 min before the procedure.

The optimal degree and duration of preoxygenation is currently not known (Oh and Seo 2003). Branson et al. (1993) suggested that patients should receive 100 % inspired O_2 for >30 s prior to suctioning. Hodge (1991) suggested increasing the FiO_2 by 10–20 % higher

Table 24.1 Main findings of studies comparing open- and closed-system suctioning in adults, paediatric patients, and neonates

Reference	Study type	Patient group	Sample size (<i>n</i>)	Main finding
Hoellering et al. (2008)	Randomised crossover	Neonates	30	Both OES and CSS resulted in variable and transient desaturation, reductions in heart rate, and lung volume changes which were not significantly different between the two methods
Heinze et al. (2008)	Randomised crossover	Adult	20	No difference in functional residual capacity loss following three suctioning methods (CSS during pressure-controlled and volume-controlled ventilation and OES)
Peter et al. (2007)	Meta-analysis	Adults	9 RCTs. <i>n</i> = 1,292	No difference between OES and CSS on incidence of VAP or mortality
Jongerden et al. (2007)	Meta-analysis	Adults	15 RCTs. <i>n</i> = 1,436	No difference between OES and CSS on incidence of VAP or mortality
Vonberg et al. (2006)	Meta-analysis	Adult	9 RCTs. <i>n</i> = 1,292	No difference between OES and CSS on incidence of VAP
Freytag et al. (2003)	Prospective randomised controlled	Adults	23	Increase in lower respiratory tract colonisation if CSS catheter unchanged for 72 h
Choong et al. (2003)	Randomised crossover	Paediatric	14	Total lung volume loss and desaturation greater with OES
Kalyn et al. (2003)	Randomised crossover	Neonates	200	CSS maintained better physiological stability, and recovery time was reduced
Woodgate and Flenady (2003)	Systematic review	Neonates	2 RCTs. <i>n</i> = 22	Insufficient evidence available
Cordero et al. (2000)	Prospective randomised controlled	Preterm neonates	175	No benefit of CSS for a number of outcome measures
Morrow et al. (2012)	Nonrandomised controlled trial	Paediatric	250	No benefit of CSS on incidence of VAP, PICU stay, duration of ventilation, or mortality

CSS closed-system suctioning, OES open-endotracheal suctioning, VAP ventilator-associated pneumonia, RCTs number of included randomised clinical trials, PICU paediatric intensive care unit

than the baseline fraction of inspired oxygen (FiO₂) for about 1 min before suctioning. Neither of these recommendations is supported by high-level evidence.

Due to the known risks of hyperoxia, it is essential that FiO₂ be returned to pre-suctioning levels as soon as the SaO₂ has stabilised.

24.3.7 Suction Catheter Size

If a catheter largely or completely occludes an artificial airway or bronchus, the full suction pressure may be transmitted to that airway leading to atelectasis (Morrow et al. 2004, 2006;

Rosen and Hillard 1962). Therefore, the most severe lung volume changes are likely to occur during ET suctioning of young infants intubated with small internal diameter ETT, as in these patients, the catheters used will always be relatively large compared to the ETT size. The suction catheter chosen should therefore be large enough to effectively suction thick secretions but not so large that it traumatises the mucosa or occludes the ETT (Singh et al. 1991).

In a prospective study of 17 ventilated paediatric patients, Singh et al. (1991) found that significant changes in SaO₂, heart rate, and intracranial pressure occurred during ET suctioning regardless of the catheter diameter. A catheter

Table 24.2 A proposed guideline for suction catheter selection

Age	Weight (kg)	ETT (mm ID)	Catheter size (FG)		
			Liquid	Medium	Thick
0–3 months	3.5	3.5	5	6	7
3 months	6	3.5	5	6	7
1 year	10	4.0	6	7	7
2 years	12	4.5	6	7	8
3 years	14	4.5	6	7	8
4 years	16	5.0	7	8	8
6 years	20	5.5	7	8	8
8 years	24	6.0	8	10	10
10 years	30	6.5	8	10	12
12 years	>30	7.0	8	10	12

mm ID mm internal diameter, *FG* French gauge

with outer diameter: ETT inner diameter of 0.7 was found to be the easiest to introduce into the ETT and was most effective in clearing secretions (Singh et al. 1991).

The recommendation for catheter size selection presented in Table 24.2 (Morrow and Argent 2008) has not been subjected to rigorous testing by means of a prospective controlled clinical trial. It is recommended that this be used as a guideline until stronger evidence is available.

24.3.8 Vacuum Pressure

When selecting suction pressures the balance between effective suctioning of secretions and potential risk to the patient must be considered. The suction pressure should be high enough to be effective in removing secretions but not so high that it causes mucosal damage or lung volume loss. There is still no high-level evidence supporting a maximum safe and effective suction level.

The findings of an observational paediatric study suggest that suctioning in the presence of ETT secretions may not result in loss of lung volume (Morrow et al. 2006) because negative pressure in the lungs produced during suctioning would only occur whilst air was flowing through the suction catheter. As soon as secretions are drawn into the catheter, the pressure in the lungs would return to that of the atmosphere (Rosen and Hillard 1962). However, routine suctioning, which often occurs in the absence of secretions,

is likely to cause significant atelectasis. Therefore, although suction pressures should be limited, the issue may not be as critical when suctioning only when indicated to do so in the presence of secretions.

Results of an animal study showed that mucosal trauma occurred when using suction pressures of both 100 and 200 mmHg; however, damage was greater at the higher suction level. This study also suggested that efficiency of aspiration was not affected by the suction pressure used (Kuzenski 1978). Conversely, in an in vitro study, it was shown that suction pressures up to –360 mmHg measured at the vacuum source were more effective in removing secretions than using vacuum pressures of ~ –200 mmHg (Morrow et al. 2004). These suction pressures were the lowest two options on the commercially available suction units in use at the time of these investigations.

Most authors advocate a range of suction pressures from 70 to 150 mmHg (Hodge 1991; Kacmarek and Stoller 1995). Young (1984) suggested that these pressures may be increased to 200 mmHg (27 kPa) to aspirate thick secretions. Singh et al. (1991) did not show any difference in the change of physiological parameters when suctioning children using vacuum pressures of 80, 100, or 120 mmHg. Clinical studies have not comparatively investigated the effects of higher suction pressures on physiological changes, efficacy of secretion removal, or patient outcome.

The potential impact of high suction pressures (potential mucosal damage and lung volume

loss) needs to be weighed against the potential damage that may occur with repeated suction passes when using an inadequate vacuum level.

24.3.9 Sterility

There is a risk of introducing pathogens into the respiratory tract during ET suctioning, largely as a result of environmental exposure of the suction catheter (Cobley et al. 1991). Therefore, it has been suggested that a strictly aseptic technique be used during ET suctioning (Branson et al. 1993; Wood 1998). During ET suctioning, however, the catheter is passed through an unsterile port, which may be colonised with potentially pathogenic organisms, into the ETT. This will occur regardless of sterility. A randomised controlled trial of 486 intubated children and infants found that reusing a disposable suction catheter in the same patient over a 24-h period did not affect the incidence of nosocomial pneumonia (Scoble et al. 2001).

The emergence of multidrug-resistant organisms in the PICU setting and the spread among patients pose the threat of outbreaks of untreatable infectious diseases with significant associated mortality and morbidity. Use of infection control precautions to prevent transmission among patients is, therefore, a top priority (Siegel 2002). Considering that transmission of infectious organisms from patient to patient frequently occurs on the hands of healthcare workers (Siegel 2002), hand washing before and after patient contact is essential despite the wearing of gloves and regardless of suctioning method (open or closed). There is also a risk of infection to the person performing ET suctioning (Curtis et al. 1999; Rabalais et al. 1991). Standard and transmission-based precautions are the only preventive measures for minimising this risk (Siegel 2002).

The recommended contact and standard precautions for patients with presumed infectious diseases include the use of gloves (either 'clean' or sterile); face protection (face masks and goggles) for open-ET suctioning, which is likely to cause splashes or sprays of secretions; washing hands before and after donning gloves;

and wearing a gown to protect the skin and prevent contamination of the clothes (Siegel 2002). Specific pathologies may require more complex barrier protection.

Although the same suction catheter may be used for several suction passes (Scoble et al. 2001), external environmental contamination should be limited. The suction catheter should be immediately discarded if it comes into contact with any surfaces and should not be used to suction the nose or mouth before introduction into the ETT.

24.3.10 Duration of Suctioning

Increasing the duration of suction application significantly increases the amount of negative pressure within a lung model (Morrow et al. 2004) and has been implicated in the degree of hypoxia induced (Rosen and Hillard 1962; Brandstater and Muallem 1969). Although there is currently no strong evidence supporting an appropriate duration of suctioning, most authors recommend between 10 and 15 s (Branson et al. 1993; Young 1984). Runton (1992) suggests that the actual time of negative pressure application during each suctioning event be limited to ≤ 5 s.

24.3.11 Depth of Catheter Insertion

The depth of insertion of the suction catheter during ET suctioning varies according to institutional practice (Spence et al. 2003). In shallow ET suctioning, the catheter is passed to the tip of the ETT, whereas in deep ET suctioning, the catheter is passed beyond the ETT into the trachea or bronchi, usually until resistance is felt.

Neonatal and animal studies have not shown any benefits of deep ET suctioning, but they have suggested increased mucosal trauma with deep suctioning (Spence et al. 2003; Bailey et al. 1988; Youngmee and Yonghoon 2003; Ahn and Hwang 2003). Mucosal inflammation as a result of deep ET suctioning could cause squamous metaplasia, ulceration, and formation of obstructive granulation tissue (Nagaraj et al. 1980). Cases of pneumothorax have been reported following deep ET

suctioning (Loubser et al. 1989; Anderson and Chandra 1976). Patients themselves are likely to prefer the sensation of shallow suctioning.

In specific situations, such as following surgical repair of tracheo-oesophageal fistulae, deep suctioning may be hazardous as the surgical site may be compromised by direct catheter trauma.

24.3.12 Use of Saline

Instillation of isotonic saline (sodium chloride) is still practised in many PICUs, under the impression that the fluid aids in the removal of pulmonary secretions by lubricating the catheter, eliciting a cough and diluting secretions. A consensus study among respiratory physiotherapists in the United Kingdom showed that most physiotherapists use normal saline when there is sputum retention and to enhance a cough where secretions cannot be successfully removed by other techniques (Roberts 2009).

Mucus and water in bulk form are immiscible and maintain their separate phases even after vigorous shaking (Demers and Saklad 1973). Thus, the function of saline as a secretion dilutant is doubtful.

It has been suggested that instillation of normal saline in conjunction with ET suctioning may result in additional dispersion of contaminated adherent material in the lower respiratory tract, with the subsequent increased risk of nosocomial infection (Freytag et al. 2003; Hagler and Traver 1994). However, a randomised trial of 162 adults (average age 64 years, duration of ventilation 11 days) showed that saline instillation was associated with a significant reduction in the incidence of microbiologically proven VAP, with a relative risk reduction of 54 %. This was attributed to better airway clearance, possibly by stimulation of coughing, and a reduction in the ETT biofilm. The incidence of atelectasis and ETT occlusion was similar between groups (Caruso et al. 2009). This study has not been replicated in other populations, and similar studies have not been done in the paediatric age group.

Adult studies have consistently reported the adverse effect of saline instillation on arterial oxygenation (Akgul and Akyolcu 2002; Ji et al.

2002; Ackerman and Mick 1998; Kinloch 1999). A randomised controlled trial of 24 paediatric patients, for 104 suctioning episodes, showed that patients who received between 0.5 and 2 ml of normal saline prior to or during suctioning experienced significantly greater oxygen desaturation than patients who did not receive saline instillation. There were no cases of ETT occlusion in either group (Ridling et al. 2003). In infants, routine saline instillation before suctioning was only found to maintain ETT patency with 2.5 mm internal diameter ETT, but no benefit was found in using saline for a 3.0 or a 3.5 mm ETT (Drew et al. 1986).

Despite the body of knowledge indicating that instillation of saline is unlikely to be beneficial and may in fact be harmful, there is still limited evidence in the paediatric population, and many clinicians continue to be concerned about adequately clearing thick secretions from small ETTs (Ridling et al. 2003). Hodge (1991) suggested that if it was deemed necessary in the case of tenacious secretions, 0.1–0.2 ml/kg body weight of 0.9 % saline could be instilled before suctioning. Shorten et al. (1991) showed that clinically stable newborn infants tolerated 0.25–0.5 ml saline instilled before suctioning.

In order to ensure that pulmonary secretions are easily manageable with suctioning, it is essential to ensure adequate humidification of inspired gas (Branson et al. 1993; Branson 2007).

24.3.13 Recruitment Manoeuvres Performed After ET Suctioning

Recruitment manoeuvres (RM) have been suggested as a method of reversing suctioning-induced lung volume loss and improving arterial oxygenation, by reinflating the collapsed lung segments before resuming ventilation (Matthews and Noviski 2001; Suh et al. 2002; Lindgren et al. 2004; Kasim et al. 2009). A RM refers to the application of a sustained inflation pressure to the lungs for a specified duration in order to return the lung to normal volumes and distribution of air.

Animal studies have reported that RM performed after ET suction completely reversed airway narrowing and atelectasis caused by

suctioning (Lu et al. 2000; Kasim et al. 2009; Russell et al. 2002). A small prospective randomised controlled study of eight adults with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) concluded that a RM performed after ET suctioning was well tolerated and produced a rapid recovery in end-expiratory lung volume, respiratory system compliance, and PaO₂. The study was limited by the small sample size (Dyhr et al. 2003).

A prospective randomised controlled trial investigated the effect of a post-suctioning RM in 34 ventilated infants and children with variable lung pathology (Morrow et al. 2007). The RM was performed by manually applying a sustained inflation pressure of 30 cm H₂O for 30 s. The RM appeared to improve airway resistance and oxygenation, but generally had no effect on dynamic compliance as compared to the control group. In both patient groups pulmonary compliance dropped significantly after open-ET suctioning, indicating a loss of lung volume. However, in most cases pulmonary compliance had returned to baseline levels within 10 min of the suctioning procedure, regardless of whether a RM was applied or not. The efficacy of the RM may have been influenced by the manual nature of the technique, specifically the likely derecruitment caused on disconnection from the ventilator before the RM. Most of the patients studied had ARDS or ALI by definition, but these were all cases of pulmonary (primary) lung injury (Morrow et al. 2007). It has previously been found, in adults, that patients with extrapulmonary ARDS showed a greater increase in PaO₂ after RM than those with pulmonary ARDS (Lim et al. 2003). Other studies investigating the use of RM in paediatric patients have involved small sample sizes and used subjects with normal lungs (Tusman et al. 2003; Marcus et al. 2002).

Kerem et al. (1990) concluded that pre-suction hyperinflation (five breaths over 10 s administered at approximately twice the patient's tidal volume), without preoxygenation, did not prevent the subsequent drop in PaO₂; however, hyperinflation after suctioning immediately restored PaO₂ to pre-suction levels. Considering that preoxygenation alone completely prevented the fall in PaO₂ with suctioning, one needs to question

the recommendation made by the authors to use post-suction hyperinflation manoeuvres in addition to preoxygenation (as this approach was not compared to others in this study), especially when one considers the potential risks of hyperinflation in the paediatric population. Whilst hyperinflation performed between suction passes may restore oxygenation to baseline levels, it will not prevent hypoxia from occurring during suctioning.

The challenge in performing RM is that the pressure required to re-expand collapsed alveoli is variable, as the pressure applied by the manoeuvre and the actual pressure delivered to the lung may differ substantially depending on a number of factors, including chest wall compliance (Grasso et al. 2002) and the nature of lung injury (Pelosi et al. 1999). Cardiovascular complications of RM have also been reported, including reduction in mean arterial blood pressure and cardiac output (Grasso et al. 2002).

Although further investigation is clearly necessary, the routine practice of performing manual RM after ET suctioning does not appear to be beneficial, and may in fact be harmful, and is therefore not justified routinely after suctioning. Further research is required to assess the value of post-suction RM performed using the ventilator without disconnection.

24.4 Evidence-Based Clinical Recommendations

Table 24.3 presents clinical practice guideline, using the following levels of evidence and grades of recommendations:

1.	A	Systematic reviews/meta-analyses
	B	Randomised controlled trials
	C	Other clinical experimental designs
2.	A	Cohort control studies
	B	Case-control studies
3.	A	Consensus conference
	B	Expert opinion
	C	Observational clinical study
	D	Other types of study (e.g. laboratory)
	E	Quasi-experimental, qualitative design
4.		Personal communication

Table 24.3 Clinical recommendations for chest physiotherapy and endotracheal suctioning of infants and children

Clinical practice	Recommendation	Grade of recommendation
Analgesia	CPT and ET suctioning cause pain and discomfort. As suctioning is often performed immediately after secretions are detected, there may be insufficient time to administer analgesia and allow it to take full effect. Therefore, it is recommended that all ventilated patients receive regular or infused analgesia for the duration of ventilation. Additional analgesia may be required prior to CPT	ET suctioning: 1B. Extrapolated from neonatal RCT (Pokela 1994) CPT: 3B. No experimental evidence
Monitoring	Considering the known complications of CPT and ET suctioning, the patient's heart rate, blood pressure, and oxygen saturation should be carefully monitored at all times during the procedure. Clinical observations should include patient colour (to detect early cyanosis), signs of respiratory distress (such as sweating, tachypnoea, marked costal recessions), and signs of pain or anxiety	3B. No experimental evidence
Indications for CPT	Routine CPT should not be provided CPT should be considered for the management of acute atelectasis caused by mucus plugging CPT may be beneficial for clearing retained secretions	1B. Paediatric RCT of cardiac surgery patients (Reines et al. 1982) 3C. Paediatric observational studies (Schechter 2007; Peroni and Boner 2000; Bilan et al. 2009; Galvis et al. 1994) 1B. Paediatric RCT (Main et al. 2004)
Postural drainage	The head-down inverted position should not be used due to potential dangers Positioning should consider the relationship between optimisation of ventilation/perfusion ratios, oxygenation, and gravity-assisted secretion drainage	1B. Extrapolated from paediatric RCTs in non-ventilated population (Vandenplas et al. 1991; Button et al. 2003); observational studies in neonates (Crane et al. 1978; Emery and Peabody 1983) 3B. No experimental evidence
Mobilisation	Appropriate mobilisation for the patient's age and condition may be considered	3B. No experimental evidence
Manual CPT techniques	Percussion and vibration may be used with care to assist mucociliary clearance	3B. No experimental evidence
Manual hyperinflation	Manual hyperinflation should not be used standardly during CPT, but may be considered only in cases of lung collapse not responsive to standard CPT modalities. When given, peak inspiratory pressure and inspired tidal volume should be carefully controlled	3C. Paediatric observational study (Galvis et al. 1994) and extrapolated evidence from animal, adult, and paediatric studies on lung injury (Dreyfuss and Saumon 1998; Brochard et al. 1998; Carpenter 2004)
Frequency of suctioning	Routine suctioning should be avoided (Loubser et al. 1989; Dyhr et al. 2003), with the possible exception of paralysed patients. Suctioning should be performed only when clinically indicated (Branson et al. 1993)	3B. No experimental evidence
Suctioning system	Although there may be short-term benefits of closed-system suctioning in terms of reduced lung volume loss and hypoxia (Choong et al. 2003), there is no clear benefit for the use of closed- or open-system suctioning, and practitioners should continue with the method at which they are proficient	1A. Extrapolated from adult (Jongerden et al. 2007; Peter et al. 2007; Vonberg et al. 2006) and neonatal (Cordero et al. 2000) systematic reviews

(continued)

Table 24.3 (continued)

Clinical practice	Recommendation	Grade of recommendation
Preoxygenation	Considering the short-term effects of hyperoxygenation in reducing hypoxia, patients should receive increased inspired oxygen levels for a brief period (≤ 60 s) prior to suctioning and during CPT. The optimal level of preoxygenation is not known but can be individually determined by the patient's clinical condition and response to handling. The clinical context should be taken into consideration, as some pathological processes may make an individual more susceptible to the adverse effects of hypoxaemia (e.g. severe pulmonary hypertension)	1C. One paediatric randomised crossover trial (Kerem et al. 1990); recommendation extrapolated from neonatal (Pritchard et al. 2003) and adult (Oh and Seo 2003) systematic reviews
Suction catheter size	Table 24.2 can be used as a guideline for suction catheter selection. Doubling the ETT internal diameter gives an indication of which FG catheter size to use for efficacy and safety (e.g. with a 3.5 mm internal diameter ETT, a size 6 or 7 FG catheter could be used)	3D. In vitro study (Morrow et al. 2004)
Vacuum pressure	Medical and paramedical staff should use the lowest pressure that effectively removes the secretions, with the least adverse clinical reaction. Suction pressures should be < 400 mmHg	3B. In vitro study (Morrow et al. 2004) and expert opinion (Hodge 1991) (Kacmarek and Stoller 1995; Dyhr et al. 2003; Bethune et al. 1971)
Sterility	A strictly sterile technique is not necessary, but staff should adhere to strict infection control measures to protect themselves and other patients (Siegel 2002; Curtis et al. 1999; Rabalais et al. 1991)	1B. Large RCT of infants and children (Scoble et al. 2001)
Duration of suctioning	In order to limit the adverse effects of lengthy duration of suctioning, and to minimise airway trauma, the catheter should be inserted in the absence of vacuum pressure and suction only applied on catheter withdrawal. The application of suction should be limited to ≤ 10 s. Patients should be reconnected to the ventilator and given several recovery breaths before repeating the suctioning procedure if secretions have not been adequately cleared by the previous suctioning event	3B. In vitro study (Morrow et al. 2004) and expert opinion (Branson et al. 1993; Runton 1992; Young 1984)
Depth of catheter insertion	Considering that there are no known benefits to performing deep ET suctioning and there is an increased risk of direct trauma and vagal nerve stimulation with deep rather than shallow suctioning, the catheter should only be passed to the end of the ETT. The depth of insertion can be determined by direct measurement	1C. Extrapolated from randomised crossover studies in high-risk neonates (Youngmee and Yonghoon 2003; Ahn and Hwang 2003)
Use of saline	Saline should never be used routinely for suctioning	1B. Paediatric RCT (Ridling et al. 2003)
When to discontinue suctioning	Suctioning should be discontinued if there are no more secretions in the large airways, if the child desaturates to ≤ 80 % (assuming baseline $\text{SaO}_2 \geq 90$ %), if the child experiences cardiac arrhythmia or bradycardia, or if the child becomes extremely agitated (respiratory signs of distress, anxiety, or pain responses). Where possible, suctioning should be discontinued if the child has acute pulmonary haemorrhage or pulmonary oedema. At all times, however, a patent airway must be ensured. In the event of hypoxia or bradycardia, the appropriate paediatric life support measures should be implemented	3B. No experimental evidence
Recruitment manoeuvres	Manual recruitment manoeuvres should not be performed routinely after endotracheal suctioning	1B. Paediatric RCT (Morrow et al. 2007)

Conclusions

CPT and ET suctioning should not be considered routine procedures in the PICU. Both have the potential for serious adverse consequences, and therefore care should be taken in assessing the need for intervention, taking into account the child's age, condition, and the presence of contraindications or precautions. The modalities used should be carefully selected and applied in order to minimise or prevent complications. Currently, objective evidence in support of clinical practice recommendations is limited. Controlled clinical trials are necessary in order to develop evidence-based protocols for CPT and ET suctioning of infants and children and to examine the impact of different modalities on patient outcome.

Until such evidence becomes available, '... those involved in the management of paediatric respiratory disorders should avoid the unnecessary distress to both the child and family of useless treatment and the potentially serious consequences of inappropriate intervention' (Wallis and Prasad 1999).

Essentials to Remember

- CPT and ET suctioning should not be considered routine procedures in the PICU. Both have the potential for serious adverse consequences, and therefore care should be taken in assessing the need for intervention, taking into account the child's age, condition, and the presence of contraindications or precautions.
- The routine practice of performing manual recruitment manoeuvres after ET suctioning does not appear to be beneficial, and may in fact be harmful, and is therefore not justified routinely after suctioning.
- The potential benefits of respiratory therapy and endotracheal suctioning are not supported by high-level evidence.
- Complications of both endotracheal suctioning and chest physiotherapy are numerous and potentially severe. Continuous monitoring is therefore necessary to ensure patient safety.
- Tracheal suctioning may be needed in all intubated and ventilated infants and children to maintain a patent airway, and therefore there can be no absolute contraindications to this practice.
- Tracheal suctioning should not be performed routinely, rather when indicated in the presence of obstructive secretions in the airways.
- There is no clear evidence for the superiority of closed- or open-system suctioning or for appropriate vacuum pressures and suction catheter size.
- Strict aseptic technique is not necessary when suctioning. Preoxygenation has short-term benefits, but the longer-term impact is unknown. Routine saline instillation before suctioning should not be performed. Recruitment manoeuvres performed after suctioning have not been shown to be useful as standard practice.
- Considering the known complications of chest physiotherapy, and lack of evidence supporting the benefits of this intervention, treatment should only be considered when there are no contraindications and retention of secretions is causing lung or lobar collapse, impacting on gas exchange or lung mechanics, and/or where there is the potential for serious long-term consequences.
- Chest physiotherapy modalities such as positioning, manual therapy (vibration and percussion), and mobilisation may be considered to aid secretion clearance and optimise ventilation and perfusion.
- Head-down postural drainage positions should be avoided. Manual hyperventilation should not be practised standardly in young infants and children due to potential volutrauma and lung injury.

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25.1 Fluid Management in the Preterm Neonate

Anne Greenough

Educational Aims

- To describe methods of assessing fluid balance in prematurely born infants
- To discuss the evidence for the type and magnitude of fluid given to prematurely born infants

Fluid balance in the sick, prematurely born must be carefully monitored; this includes hourly recording of all fluid input and output and at least daily weights. Prematurely born infants have a limited capacity to excrete a sodium load; sodium supplementation should be delayed until the onset of postnatal extracellular volume contraction. Colloid infusions should be used sparingly in sick, preterm infants; data from randomized trials have highlighted safer and at least equally effective alternatives, for example, in the treatment of hypotension. Fluid restriction in the perinatal period reduces morbidity.

25.1.1 Introduction

Fluid management of the prematurely born infant must reconcile the need to “grow the infant,”

while too much fluid may increase morbidity including patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), and bronchopulmonary dysplasia (BPD); too little fluid may exacerbate electrolyte and metabolic disturbances, even acute renal failure. The sick, prematurely born infant’s fluid management is particularly complex for a number of reasons. Prematurely born infants have a high trans-epidermal water loss due to their skin immaturity and a large surface area to weight ratio; trans-epidermal water loss can be compounded if infants are nursed naked under a radiant warmer. In all infants, shortly after birth, there is a contraction of the extracellular compartment due to the loss of interstitial fluid, which is associated with postnatal weight loss (Modi et al. 2000). The timing of the diuresis/natriuresis, however, is related to the fall in the pulmonary vascular resistance, which may be variable in sick, prematurely born infants. Prematurely born infants have immature renal function, and in addition, respiratory water loss is influenced by the level of humidification of the inspired gases in ventilated infants. They may also be exposed to therapies that affect their fluid balance. For example, the majority of mothers of prematurely born infants will have been given antenatal corticosteroids in an attempt to improve lung immaturity, and antenatal corticosteroids may enhance fetal epithelial cell maturation and improve skin barrier function (Omar et al. 1999; Dimitriou et al. 2005). This results in lower insensible water loss and a higher urine output (Dimitriou et al. 2005). In this

section, assessments of fluid balance are reviewed and the evidence for the type and magnitude of fluid given to prematurely born infants is discussed.

25.1.2 How to Assess Fluid Balance Status?

Fluid intake should be carefully recorded on an hourly basis, including all crystalloid and colloid input, plus medications and “flush” volumes. Urine output needs also to be accurately determined. One method is to collect urine output on open nappies, and for extremely low birth weight infants, cotton wool balls are placed on the nappy (Kavvadia et al. 2000a). As soon as the infant voids, the nappy or cotton wool ball should be weighed; otherwise, the volume may be underestimated due to losses from evaporation. An alternative method is to use a urine bag and aspirate urine with a fine catheter from the bag as soon as the urine is voided (Hartnoll et al. 2000). It is important, if the infant appears to be oliguric, to check that the bladder is not palpable. The magnitude of fluid input should be reduced if the infant develops acute renal failure defined as for any 24-h period a creatinine level greater than 132 $\mu\text{mol/l}$ and urine output less than 1.0 ml/kg/h, except one day when a urine output of less than 0.5 ml/kg/h may indicate acute renal failure. Urine osmolality should also be measured; a level of between 200 and 400 mOsm/kg suggests a satisfactory fluid intake. Immature infants, however, have a limited ability to concentrate their urine and may pass urine of low osmolality while becoming dehydrated; hence, it is important to concurrently check the infant’s weight. Infants should be weighed on a daily basis, which is greatly facilitated by use of “bed” scales which remain inside the incubator and the infants are nursed upon them; hence, minimal handling is required to assess the weight.

Electrolytes and creatinine should be measured at least on a daily basis and more frequently

if the infant is developing or has developed renal failure. Creatinine is derived from phosphocreatine in muscle and excreted in urine and is used as an index of the glomerular filtration rate (GFR). The serum level at birth reflects the maternal concentration. Creatinine clearance and the GFR increase with increasing postnatal age in premature infants (Gallini et al. 2000). Serum creatinine falls in the first week after birth as the maternally derived creatinine is excreted; therefore, failure to see the expected decline or a rise in the creatinine level indicates a reduced GFR.

25.1.3 Which Fluids?

Sodium supplementation should be delayed until the onset of postnatal extracellular volume contraction, which is indicated by marked weight loss (Modi et al. 2000). Prematurely born infants have a limited capacity to excrete a sodium load (Robillard et al. 1992), and in a randomized trial which included 25–30-week gestation infants, early (4 mmol/kg/day from the second day) compared to delayed (when weight loss of 6 % of birth weight had been achieved) supplementation was associated with delayed loss of body water (Hartnoll et al. 2000). In addition, by the end of the first week, 35 % of the babies in the delayed group but only 8.7 % of the early intake group no longer required supplementary oxygen (Hartnoll et al. 2000).

Colloid infusions should be used sparingly in sick, preterm infants, not least as there may be a safer, cheaper, and an at least equally effective alternative (Greenough 1998). In a randomized trial, isotonic saline and albumin were equally as effective in reducing the hematocrit in polycythemic infants (packed cell volume greater than 65 %) (Wong et al. 1997). Colloid infusions should not be used as first-line treatment for hypotension as several studies have demonstrated it is the volume infused rather than the protein load which is more efficacious in treating hypotension (Greenough 1998). In addition, in a

randomized trial, isotonic saline was equally as effective as a similar volume of colloid in treating hypotension (So et al. 1997). Indeed, results highlight crystalloid may be more appropriate to treat hypovolemic hypotension, as the infants given albumin had significantly higher weight gain in the first 48 h, suggesting they suffered fluid retention (So et al. 1997). Albumin should not be given as part of the initial resuscitation process, as low Apgar scores may indicate myocardial depression in which case volume load is contraindicated. Asphyxia also results in increased capillary permeability and protein leak into the lung could impair resuscitation (Jobe et al. 1985). Furthermore, we have demonstrated that the amount of colloid infused in the perinatal period significantly correlated with the duration of oxygen dependency (Kavvadia et al. 2000a) and abnormal perinatal lung function (Marks et al. 1978). Colloid was prescribed to hypotensive infants (Kavvadia et al. 2000a) and thus it might be that the adverse outcomes were related to the severity of the underlying illness rather than colloid infusion per se. An alternative explanation, however, is that when colloid is given to infants with increased vascular permeability, it leaks into the lungs, worsening respiratory function (Marks et al. 1978) and necessitating higher levels of respiratory support, and hence could predispose to BPD. There are also no data to support the use of albumin infusion to “treat” low serum albumin levels. Two randomized, but small trials have been performed with no differences in mortality or morbidity (Jardine et al. 2010). In one of the studies (Greenough et al. 1993), albumin infusion was associated with a significant increase in the albumin level and a reduction in weight, but no significant changes in the peak inflating pressures.

25.1.4 How Much Fluid?

Excessive fluid input increases the likelihood of PDA and BPD development. In a retrospective

analysis of data from 1,382 ELBW infants of birth weight between 401 and 1,080 g, multivariate logistic regression demonstrated that higher fluid in the infant and less weight loss during the first 10 days were significantly related to death or BPD (Oh et al. 2005). Yet administration of diuretics to infants with RDS results in no long-term benefits and only transient improvements in lung function (Brion and Soll 2011). An alternative approach has been to use fluid restriction to try and prevent morbidity and mortality in prematurely born infants. There has been a number of randomized trials comparing restricted versus liberal water intake. Meta-analysis of five such studies (Bell and Acarregui 2008) demonstrated that restricted water intake increased postnatal weight loss and significantly reduced the risks of PDA and necrotizing enterocolitis (NEC), but not BPD and intracranial hemorrhage (ICH). In only one of the studies, however, were antenatal steroids and postnatal surfactant given routinely (Kavvadia et al. 2000a). That study (Kavvadia et al. 2000a) demonstrated no statistically significant differences in PDA, ICH, NEC, or BPD, but significantly more (43 % versus 19 %) of the liberal versus restricted group received postnatal corticosteroids, as it was considered they were at high risk of developing BPD. Importantly, there were no statistically significant differences in the incidence of acute renal failure (Kavvadia et al. 2000a) or electrolyte or metabolic disturbances (Kavvadia et al. 2000b). Those results (Kavvadia et al. 2000a, b) support the conclusion in the Cochrane review (Bell and Acarregui 2008) that the most prudent prescription for water intake of prematurely born infants is careful restriction of water intake so that physiological needs are met without allowing significant dehydration. Whether fluid restriction is beneficial in specific situations remains to be appropriately tested. One of three Cochrane reviews at the protocol stage has now been reported and demonstrated no eligible trials.

Future Perspectives

- More accurate techniques to assess fluid balance in extremely low birth weight infants need to be devised.
- Further studies are required to determine the most appropriate amounts of fluid input in the present population of extremely low birth weight infants.

Essential to Remember

- In the perinatal period, prematurely born sick infants should be fluid restricted, but ensuring their physiological needs are met without significant dehydration.
- Sodium supplementation should be delayed until the onset of postnatal extracellular volume contraction, which is indicated by marked weight loss.
- Colloid infusions should be used sparingly in sick, preterm infants.

25.2 In the Pediatric Patient

Stacey Valentine and Adrienne G. Randolph

Educational Aims

- To understand the pathophysiology of fluid transport in the healthy and injured lung
- To understand the implications of fluid management in the mechanically ventilated child with respiratory failure
- To identify the key outcomes of fluid overload in patients at risk for and with acute lung injury
- To identify the key differences in fluid management in acute lung injury with and without shock
- To understand how the type of fluid administered may impact clinical outcomes

25.2.1 Fluid Management in the Mechanically Ventilated Patient

The challenge of fluid management in critically ill pediatric patients with respiratory failure is to maintain intravascular volume to ensure adequate end-organ perfusion while minimizing extravascular lung water and subsequent pulmonary edema (Ware and Matthay 2000; Wiedemann et al. 2006; Calfee and Matthay 2007). Mechanically ventilated pediatric patients are at risk for developing acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS). Evidence for fluid management in patients with respiratory failure is extrapolated from research on fluid management in acute lung injury. Over the past 30 years, clinical evidence has indicated that positive fluid balance is associated with worsened clinical outcomes in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) (Ware and Matthay 2000; Wiedemann et al. 2006; Calfee and Matthay 2007; Zimmerman et al. 2009; Ahmed et al. 2009; Thakur et al. 2010; McIntyre et al. 2000; Luce 1998; Schuster 1993). Both ALI and its more severe form, ARDS, are the result of a large-scale pulmonary inflammatory response, leading to hypoxemia and respiratory failure. The common pathway of this inflammatory response is diffuse alveolar damage, resulting in pulmonary edema secondary to a pulmonary endothelium and epithelium that is more permeable to water and proteins (Ware and Matthay 2000). Prevention of ALI and ARDS is key in the management of mechanically ventilated children. The major risk factor identified in pediatric patients developing ALI is severe sepsis with pneumonia as a source (Zimmerman et al. 2009). Research on prevention of ALI is sparse, with early identification tools currently under way; the focus of research in ALI and ARDS has been on understanding the pathophysiology of the disease and supportive management (Ahmed et al. 2009; Thakur et al. 2010). The challenge of fluid management

in critically ill patients with respiratory failure is to continually assess the patient's intravascular volume status and carefully titrate fluid management to maintain adequate perfusion. Once reached, it is important to carefully restrict all fluids administered to the patient, including all intravenous infusion, antibiotics, and flushes. This has led to intense debate in the optimal fluid management of patients both to prevent and to treat ALI.

Studies with pulmonary biopsies of patients with ARDS have demonstrated that interstitial and alveolar edema occur early when inflammatory cells are present in the interstitium (Ware and Matthay 2000). Animal models of ALI have suggested that lower cardiac filling pressures and intravascular pressures can limit extravascular lung water accumulation (Craig et al. 2010; Folkesson and Matthay 2006; West 2000). Patients with lower pulmonary artery occlusion pressures (PAOP) have been found to have significantly improved survival than those with higher PAOP, while studies lowering intravascular hydrostatic pressures have been shown to reduce pulmonary edema (West 2000; Ware and Matthay 2005; Schuster and Haller 1990; Sakka et al. 2002; Berkowitz et al. 2008; Cheng et al. 2005). Until 2006, fluid management was guided by observational studies and small randomized controlled trials, supporting the notion that a restrictive fluid strategy improves survival in patients with ARDS (Wiedemann et al. 2006). In 2006, the ARDS Network found a significant reduction in the duration of mechanical ventilation ($p < 0.001$), length of stay (LOS) in the intensive care unit ($p < 0.001$), and oxygenation index in patients with ALI exposed to a conservative versus liberal fluid strategy (Wiedemann et al. 2006). However, optimizing fluid management in patients with lung injury is challenging, given that ALI and ARDS are known to occur in states of sepsis and shock. The major goal of fluid management in patients with ALI and ARDS is to adequately fluid-resuscitate the patient in shock but aggressively fluid-restrict and diurese the patient when out of shock.

25.2.2 Pathophysiology

Understanding the physiology of normal fluid clearance in the lung is crucial to managing a patient's fluid status with respiratory failure (Ware and Matthay 2005; Ware 2006). Normal alveolar epithelium is composed of two types of cells, flat type I cells, which make up 90 % of the alveolar surface area, and cuboidal type II cells, which make up the remaining 10 %. Type II cells regulate ion transport, produce surfactant, and are responsible for further proliferation of type I cells (Ware and Matthay 2005). Alveolar fluid clearance across the alveolar-capillary membrane is an active process. The driving force for alveolar fluid clearance is the active transport of sodium and chloride across the alveolar epithelium and occurs primarily by ATII cells (Folkesson and Matthay 2006). Sodium uptake occurs on the apical surface through amiloride-sensitive channels and is then pumped actively from the basolateral surface into the lung interstitium by the Na-K-ATPase (Folkesson and Matthay 2006; West 2000; Ware and Matthay 2005; Schuster and Haller 1990). This fluid follows the sodium gradient by a simple osmotic mechanism, partially mediated by aquaporins. Tight junctions sustain the apical and basolateral cell polarity, thereby regulating fluid permeability (Sakka et al. 2002).

Fluid accumulates in the alveolar space when this protective mechanism fails, either by overwhelming the active reabsorption mechanism or injuring the capillary-alveolar membrane. Increased fluid accumulation secondary to a dysfunctional reabsorption mechanism can be caused by an increase in pulmonary capillary pressure or rapid shifts in thoracic pressure. Increased permeability of the capillary-alveolar barrier is commonly a result of overwhelming inflammation. Injury to the lung parenchyma, either by direct injury or indirect injury by a systemic process leading to pro-inflammatory and cytokine release, causes disruption of the tight junctions that regulate fluid movement, resulting in unregulated leakage of fluid and protein into the interstitium and alveolar space (West 2000; Ware and Matthay 2005; Schuster and Haller 1990; Sakka et al. 2002; Berkowitz et al. 2008).

25.2.3 Measuring Outcomes of Fluid Management in the Mechanically Ventilated Patient

Fluid management is crucial in the management of mechanically ventilated patients. However, measuring the outcomes of fluid management in respiratory failure can be challenging. Outcome measures include direct physiologic measurements of fluid balance in the lung, i.e. measuring extravascular lung water (EVLW) (Schuster 1993; Sakka et al. 2002; Berkowitz et al. 2008) and clinical outcome measures. Determining the target for EVLW is difficult to generalize without the clinical context (Schuster 1993). Clinical measures of fluid management in the patients with respiratory failure include duration of mechanical ventilation, measured as ventilator-free days at day 28; oxygenation index and $\text{PaO}_2/\text{FiO}_2$ ratio; and measures of non-pulmonary organ function, measured as organ-failure-free days at day 28 (Wiedemann et al. 2006). Many of these measures were used in the early clinical trials to demonstrate improved clinical outcomes with a restrictive fluid management and are summarized in Table 25.1.

25.2.4 Early Clinical Trials

In 1987, Simmons et al. (1987) demonstrated that patients with ARDS who lost more than 3 kg of weight by the 14th ICU day had significantly improved rates of survival compared to patients who gained more than 3 kg. Schuller et al. (1991) reiterated this finding in 1991, noting that positive fluid balance was an independent predictor of survival, after accounting for baseline differences in severity of illness. Patients who gained less than one liter of fluid in the first 36 h of enrollment had a significantly higher rate of survival, shorter mean duration of mechanical ventilation, and shorter ICU stay. Humphrey et al. (1990) found similar results in a retrospective analysis of 40 ARDS patients, noting improved survival in patients who achieved a directed fluid

removal regimen, with reduction in pulmonary capillary wedge pressure, compared to those without a reduction. In a study of 36 patients with septic shock and ALI, Alsous et al. (2000) demonstrated a net positive fluid balance of 500 ml or greater within the first 3 days of ICU admission was an independent predictor of mortality. In an international observational cohort study of 393 patients with ALI/ARDS by Sakr et al. (2005), patients who survived their ICU stay achieved a net negative fluid balance in the first 96 h compared to non-survivors. Positive fluid balance was found to be an independent predictor of ICU mortality, after adjusting for severity of illness.

25.2.5 FACTT and Recent Clinical Trials

These early studies paved the way for the NIH NHLBI Fluids and Catheters Treatment Trial (Wiedemann et al. 2006), a multicentered, randomized controlled trial evaluating a conservative fluid management strategy compared to a liberal fluid management strategy in patients with ALI and ARDS. Using a two-by-two factorial design, investigators simultaneously compared two fluid management strategies while evaluating the use of central venous catheters compared to pulmonary artery catheters in 1,000 patients with ARDS. The fluid and diuretic management was directed by a protocol which assigned patients to one of 20 cells based on central venous or pulmonary artery occlusion pressure and the following clinical findings: the presence or absence of shock, defined as vasopressor use; mean arterial pressure of <60 ; the presence or absence of oliguria; and the presence or absence of effective circulation.

The FACTT protocol is summarized in Fig. 25.1. It is important to note that the protocol was only applied to patients not in shock. All patients were managed with a low tidal volume, a plateau-pressure-limited strategy as defined by previous ARDS Network studies. Patients who were in shock were managed per the individual physician's discretion and were not allowed back

Table 25.1 Summary of clinical trials in fluid management

Year	Author	Entry criteria	# pts	Fluid targets	Outcomes	Independent predictor of mortality
				Protocol group	Protocol/control (<i>p</i> -value)	
1987	Simmons et al.	ARDS	111 adults	<3 kg weight gain day 14	Survival 67/0 %	N/A
1991	Schuller et al.	ARDS	36 adults	<1L (+) balance 36 h	Survival 74/50 % <i>p</i> =0.05	Yes
1990	Humphrey et al.	ARDS	40 adults	25 % reduction of Ppw	Survival 75/29 % <i>p</i> <0.02	Yes
2000	Alsous et al.	ARDS	36 adults	Negative fluid balance in first 3 days after admission	Survival 100/31 % RR 5.0 95 % CI 2.3–10.9	Yes
2005	Sakr et al.	ALI/ARDS	393 adults	Fluid balance 96 h (L) Survivors/non-survivors	Fluid balance Survivors/non-survivors 1.4±6.5/3.9±7.8 <i>p</i> =0.001	Yes
2006	Wiedemann et al.	ARDS	1,000 adults	Conservative fluid ^b vs. liberal fluid ^b protocol	Mortality 25.5/28.4% <i>p</i> =0.30 VFDs 14.6±0.5/12.1±0.5 <i>p</i> <0.001	No
2009	Rosenberg et al.	ARDS	844 adults	(–) Fluid balance day 4	Mortality OR 0.50 95 % CI 0.28–0.89 <i>p</i> <0.001 °VFDs 15+11/10+11 <i>p</i> =0.001	Yes
2009	Murphy et al.	ALI in septic shock	212 adults	AIFR and CLFM ^a CLFM ^a AIFR ^a Neither ^a	Mortality 18.3 % 41.9 % 56.6 % 77.1 % <i>p</i> <0.001	Yes
2009	Stewart et al.	ARDS	244 adults	Conservative ^b vs. restrictive protocol ^b	Mortality 25 % 28 % <i>p</i> =0.3 °VFDs 15.1±1/13.1±1 <i>p</i> =0.04	No

Outcomes of fluid management in patients with ALI and ARDS from 1987 to 2009

^aAIFR, adequate fluid resuscitation of >20 ml/kg bolus and CVP >8; CLFM, conservative late fluid management and negative fluid balance on at least two consecutive days after resolution of septic shock

^bConservative and restrictive fluid protocols are described in the text and are outlined in detail in Wiedemann et al. (2006)

^cVFD, ventilator-free days measured at day 28

into the protocol until 12 h after shock had been reversed. Patients in the conservative arm received fluid and diuretic therapies to achieve the goal CVP of <4 mmHg or PAOP of <8mmHg while maintaining a mean arterial pressure

(MAP) of >60 mmHg, effective circulation, and urine output of >0.5 cc/kg/h. Those randomized to the liberal arm received fluid and diuretic therapies to achieve a goal CVP of 10–14 or PAOP while also maintaining a MAP of >60, a urine

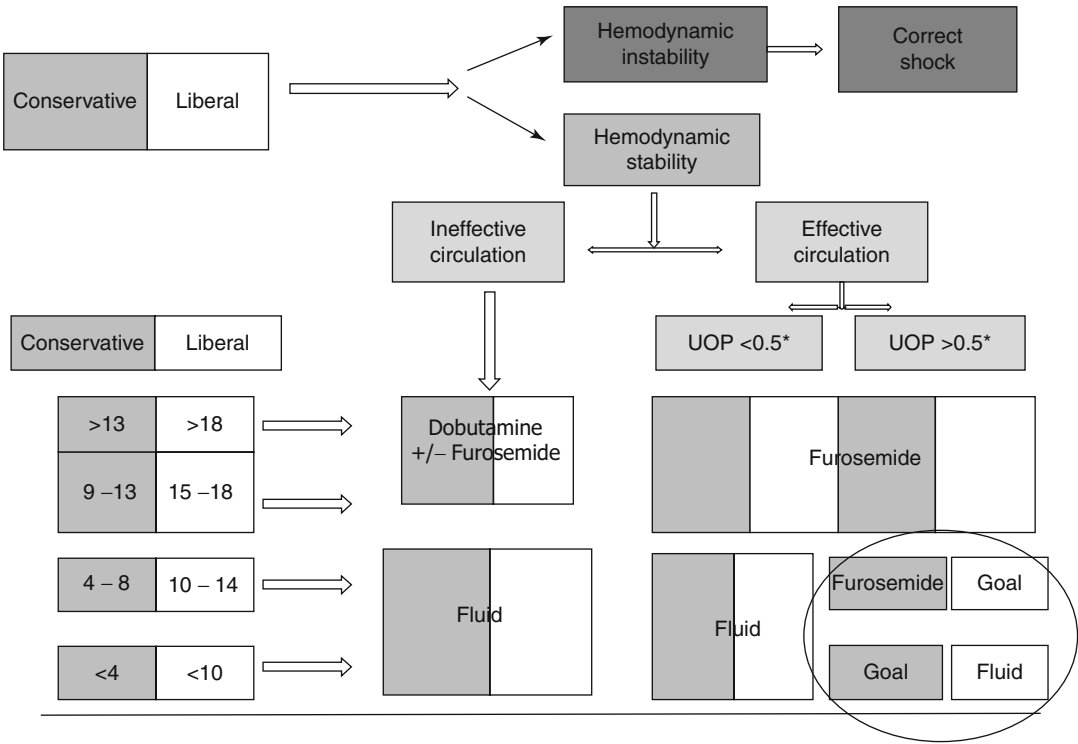


Fig. 25.1 Summary of FACTT protocol. Summary of FACTT protocol. *UOP urine output in cc/kg/h. Fluid was managed to achieve the goal cell for each treatment

group. This goal cell is shown in the lower right-hand corner of the table and was a CVP of <4 for the conservative group and a CVP of 10–14 for the liberal group

output of 0.5 cc/kg/h, and effective circulation. Patients with renal failure were excluded (Wiedemann et al. 2006).

The mean cumulative fluid balance in the conservative group at the end of 7 days was -136 ± 491 ml compared to $6,992 \pm 502$ ml ($p < 0.0001$) in the liberal group. Patients in the conservative arm had a clear improvement in pulmonary outcomes without a significant increase in non-pulmonary organ dysfunction ($p < 0.06$). Patients in the conservative arm had a significant reduction in the duration of mechanical ventilation, 14.6 ± 0.5 versus 12.1 ± 0.5 ($p < 0.001$); significant increase in oxygenation index, 10.1 ± 0.8 versus 11.8 ± 0.7 ($p = 0.003$); significant improvement in lung injury score, 2.03 ± 0.07 versus 2.27 ± 0.06 ($p < 0.001$); as well as significantly lower PEEP and plateau pressures ($p = 0.008$ and $p = 0.002$). The ICU length of stay in the intensive care unit was significantly lower

in the conservative group, and the number of central-nervous-failure-free days was significantly higher in the conservative group ($p < 0.001$). The mortality rates in the PAC and CVC groups were equivocal, 27.4 % versus 26.3 %, $p = 0.69$, and no interaction was noted between the two arms. Measures of cardiac index, stroke volume, and mean arterial pressures were slightly lower in the conservative arm, but clinically nonsignificant. Likewise, the incidence of shock and need for dialysis was similar in both groups. Patients in the conservative arm did have an increased incidence in electrolyte abnormalities, including lower potassium values and higher arterial CO_2 , arterial pH, serum sodium, and bicarbonate levels (Wiedemann et al. 2006).

As pointed out by Calfee and Matthay (Wiedemann et al. 2006; Calfee and Matthay 2007) the FACTT must be interpreted in context of the study design. It is important to note that

patients did not enter the protocol until hemodynamically stable. Patients received fluid resuscitation per the physician's discretion until the shock state was resolved. This resulted in a mean time of 43 h from ICU admission to the first protocol intervention unlike those patients in the early goal-directed therapy studies where the mean time to treatment was 1.5 h after arrival to the emergency room. This difference leads to difficulty in comparing the FACTT to early goal-directed trials (Gattinoni et al. 1995; Dellinger et al. 2008; Pope et al. 2010; Puskarich et al. 2009; Rivers et al. 2001; Rivers 2006). Finally, it is important to note that the liberal fluid strategy was reflective of usual fluid management care in patients with ARDS at the time the FACTT was performed. Patients in prior ARDS Network studies gained an average of 1 l of fluid per day (The Acute Respiratory Distress Syndrome Network 2000, 2004a, 2006).

More recently, the conservative fluid strategy was again associated with improved pulmonary outcomes in patients with ALI and ARDS. In 2009, Rosenberg et al. (2009), in a retrospective analysis of the ARDS Network ARMA study, found that a negative cumulative fluid balance at day 4 in patients with ALI was associated with significantly lower mortality, independent of other measures of severity of illness (OR, 0.50 95 %; CI, 0.28–0.89; $p < 0.001$). Patients with a positive fluid balance at day 4 had an increased length of mechanical ventilation, 13+9 versus 11+9 ($p = 0.015$); fewer ventilator-free days, 10+11 versus 15+11 ($p = 0.001$); and fewer ICU-free days, 9+10 versus 13+10, $p = 0.009$.

In a retrospective cohort study, Murphy et al. (2009) evaluated fluid management in 212 patients with ALI, complicated by septic shock. In-hospital mortality was statistically lower in patients who received adequate initial fluid resuscitation (AIFR) in shock, defined as >20 ml/kg bolus of fluid and achievement of CVP >8 mmHg, as well as conservative late fluid management (CLFM), defined as a negative fluid balance on at least two consecutive days during the first 7 days after septic shock. Mortality rates were lower in patients receiving CLFM and AIFR, 18.3 %, versus those receiving CLFM only, AIFR only, and

neither, 41.9, 56.6, and 77.1 % respectively ($p < 0.001$).

Stewart et al. (2009) in 2009 separately analyzed a cohort of surgical patients from the FACTT. Two hundred and forty-four patients were identified. Mortality did not differ in the two groups. However, the number of ventilator-free days was significantly higher in the fluid conservative group versus the fluid liberal group, 13 ± 1 and 15 ± 1 days, $p = 0.04$, with no significant increase in renal failure. These studies suggest that fluid balance in a patient with ALI and ARDS, independent of severity of illness, improves pulmonary outcomes without worsening non-pulmonary outcomes and may be a risk factor for mortality (Sevransky et al. 2009; Cooke et al. 2009).

25.2.6 Diuretic Therapy and Choice of Fluids in Acute Lung Injury

The choice of fluid to administer in critically ill patients with ALI and ARDS has also been debated (Cochrane Injuries Group Albumin Reviewers 1998; Martin et al. 2005; Liu and Matthay 2008; The Acute Respiratory Distress Syndrome Network 2004b; Cook 2004; Vincent et al. 2005; Wilkes and Navickis 2001). Studies have shown that hypoproteinemic patients tend to be twice as likely to develop ALI and ARDS and three times more likely to die after its onset (Mangialardi et al. 2000). In 2004, the Saline versus Albumin Fluid Evaluation (SAFE) trial compared the use of albumin versus normal saline in fluid resuscitation and showed similar results, irrespective of a patient's baseline serum albumin concentration (The Acute Respiratory Distress Syndrome Network 2004b). In a randomized, double-blinded study of 40 patients with ALI and ARDS, Martin et al. (2002) found that the addition of albumin to furosemide therapy in hypoproteinemic patients with ALI and ARDS significantly improves oxygenation, with greater net negative fluid balance and better maintenance of hemodynamic stability. Fliser et al. (1999) demonstrated that albumin potentiates the action of furosemide in patients with nephritic

syndrome. However, Margaron and Soni (2002) showed albumin supplementation sufficient to double serum concentrations in hypoalbuminemic septic patients had no clinically significant effect on reducing microvascular permeability. More recently, Kuper et al. (2007) showed that hyperoncotic albumin given alone or with furosemide only transiently improved oxygenation and hemodynamics.

Further studies have suggested that optimizing sodium and chloride input can improve outcomes (Gosling 2003). Interstitial edema is associated with severe sodium and water retention. Fluid resuscitation with isotonic fluids is necessary to restore intravascular volume in states of shock associated with overwhelming inflammation; however, after resuscitation is achieved, excessive sodium loads can lead to total body overload. Limiting the sodium and chloride intake and optimizing colloids once patients are no longer in shock have been associated with improved outcomes (Gosling 2003). Supranormal sodium and chloride content of normal saline, with an osmolality of 304 mOsm/kg, stimulates vasopressin release leading to further fluid retention. Hyperchloremia has been shown to cause renal vasoconstriction, which may further potentiate fluid retention and can lead to hyperchloremic metabolic acidosis (Gosling 2003). Close attention should be paid to the electrolyte balance of patients with ALI and ARDS to prevent salt overload.

Transfusion with blood products carries its own inherent risk of transfusion-related acute lung injury or TRALI (Marik and Corwin 2008). The incidence of TRALI is widespread and can occur from 1:5 to 1:10,000 transfusions (Silliman et al. 2009). Plasma-related products carry a higher risk of TRALI than packed cells, platelets, and fresh frozen plasma (FFP) alone. In a recent study by Church et al. (2009), FFP was associated with increased mortality in pediatric patients with ALI, independent of severity of hypoxemia, multiple organ system failure, or disseminated intravascular coagulopathy (DIC). Those patients transfused with FFP had a trend towards increased number of ventilator-free days. Multicentered randomized trials both in children and adults have shown that a restrictive packed red blood

cell transfusion strategy is safe in stable critically ill patients (Church et al. 2009).

25.2.7 Pediatric Data

As seen in adults, there is increasing evidence that positive fluid balance in children with ALI/ARDS is associated with worse clinical outcomes (Randolph 2009; Flori et al. 2011; Valentine et al. 2012; Willson et al. 2013; Foland et al. 2004; Napolitana et al. 2010). In a multicenter retrospective cohort study, Valentine et al demonstrated that increased fluid balance at day 3 was independently associated with increased duration of mechanical ventilation (Valentine et al. 2012). Flori et al similarly demonstrated an association between increased fluid balance at day 3 of illness and increased duration of mechanical ventilation and mortality in children with ALI (Flori et al. 2012). Finally, Willson et al, in a post hoc analysis of the multicenter randomized controlled CARDS trial, demonstrated that increased fluid balance was independently associated with fewer ventilator free days and worsened oxygenation indices (Willson et al. 2013). However, in a retrospective review of pediatric patients with ALI and ARDS by Santschi (Santschi et al. 2010), only 29 % of patients received a restrictive fluid strategy. Further studies are urgently needed to determine the safety and efficacy of a restrictive fluid management strategy in pediatric patients with respiratory failure, ALI, and ARDS as well as to identify the optimal fluids to use in critically ill children (Randolph 2009; Randolph et al. 2009).

25.2.8 Summary

Patients with acute respiratory failure are at risk for developing ALI. Positive fluid balance is clearly associated with worsened clinical outcome in adult patients with ALI and ARDS. The overwhelming inflammatory response in ALI and its more severe form, ARDS, leads to increased extravascular pulmonary water, making careful fluid management necessary. The key feature of fluid management studies in patients with ALI and ARDS is to adequately fluid-resuscitate the patient

in shock and aggressively fluid-restrict the patient when out of shock. Combined albumin and furosemide therapy is associated with improved pulmonary outcomes while blood products carry the risk of TRALI. Careful attention should be taken to monitor electrolytes and the sodium and chloride loads should be altered appropriately. The outcomes associated with fluid management in pediatric patients with lung injury are unknown and are extrapolated from adult studies. It is necessary to study the outcomes of fluid management in pediatric patients with respiratory failure, ALI, and ARDS, in a systematic fashion, through large, randomized controlled trials.

Essentials to Remember

- Fluid accumulates in the lung secondary to either an increase in pulmonary capillary pressure or increased permeability of the capillary-alveolar barrier, commonly a result of overwhelming inflammation.
- Injury to the lung parenchyma, either by direct injury or indirect injury, leads to pro-inflammatory and cytokine release, causing disruption of the tight junctions that regulate fluid movement resulting in unregulated leakage of fluid and protein into the interstitium and alveolar space.
- The key feature of fluid management in patients with lung injury is to adequately fluid-resuscitate the patient in shock and aggressively fluid-restrict the patient when out of shock. Identify the key outcomes of fluid overload in acute lung injury patients.
- A fluid restrictive strategy has been shown in randomized, multicentered trials to improve the duration of mechanical ventilation, oxygenation index, and ICU length of stay in adult patients with ALI/ARDS.
- Albumin, used with a furosemide, may improve oxygenation and fluid diuresis in adult patients with ALI/ARDS.
- Further research is needed to understand the impact of fluid management in critically ill children with ALI and ARDS.

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Part IX

Permissive Hypercapnia

Patrick Hassett, John G. Laffey,
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Educational Goals

- To focus on the role of ventilatory strategies involving permissive hypercapnia in the management of neonates and infants with acute respiratory failure
- To examine the physiologic effects of hypercapnia on the lungs and other organ systems
- To determine the potential for hypercapnia to directly modulate lung and systemic organ injury, and the mechanisms underlying these effects
- To consider the clinical role of permissive hypercapnia in neonatal and pediatric critical care
- To consider the risks and benefits of permissive hypercapnia in specific clinical situations

26.1 Introduction

The potential for high-stretch mechanical ventilation to cause ventilator-induced lung injury (VILI) and worsen the severity of ARDS is clear. Protective ventilatory strategies that reduce tidal – and minute – ventilation improve outcome in both adults (The Acute Respiratory Distress Syndrome Network 2000; Amato et al. 1998) and children (Wung et al. 1985; Mariani et al. 1999) with severely injured lungs. In fact, the potential for mechanical ventilation to injure lungs was first described in children over 30 years ago (Moylan et al. 1978). The high levels of PaCO₂ arising from ventilation with lower tidal volumes are well tolerated clinically and have been termed “permissive hypercapnia.” The benefits of ventilator strategies that incorporate permissive hypercapnia are assumed to be a result of reduced lung stretch. However, hypercapnia itself has the potential to exert beneficial – and harmful – effects. Prior to recognizing the importance of “protective” ventilator strategies, normocapnia and even hypocapnia were considered to be desirable clinical targets. The basis for previously targeting normal PaCO₂ was based on the idea

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that “normal” physiology was desirable, as well as on links between hypercapnia and poor outcomes in a number of conditions including sepsis (Balakrishnan et al. 2000; Friedman et al. 1995; Mathur et al. 1996), asphyxia (Anyaeibunam et al. 1991), and cardiac arrest (Jorgensen and Holm 1999; Suljaga-Pechtel et al. 1984).

This chapter will focus on ventilator strategies involving permissive hypercapnia in neonates and infants with acute respiratory failure. Using evidence gathered from laboratory studies, we will examine the biological effects of hypercapnia on organ systems and the modulating effects that hypercapnia has on models of systemic and lung injury. The potential for hypercapnia to exert *direct* effects on lung injury will also be considered (Laffey and Kavanagh 1999). The role of permissive hypercapnia in clinical settings that are relevant to neonatal and pediatric practice will then be discussed. Finally, the risks and benefits of permissive hypercapnia will be considered in specific clinical situations.

26.2 Physiologic Effects of Hypercapnia

In critically ill children, permissive hypercapnia should only be allowed to develop once its physiological effects have been considered. However, the direct effects of hypercapnia can sometimes be countered by indirect effects. Another area of controversy is whether hypercapnia exerts its diverse effects through an accompanying acidosis or whether the CO_2 per se is responsible. The role of buffering in permissive hypercapnia and many other questions remain incompletely answered.

26.2.1 Pulmonary System

The effects of hypercapnia on lung physiology can be broadly discussed under three main categories: airways resistance, regional perfusion, and pulmonary vascular resistance. The physiological effects of hypercapnia on airway resistance provide a good example of its sometimes complex and contradictory nature in the physiological milieu. Direct dilatation of the small airways and indirect vagally mediated large air-

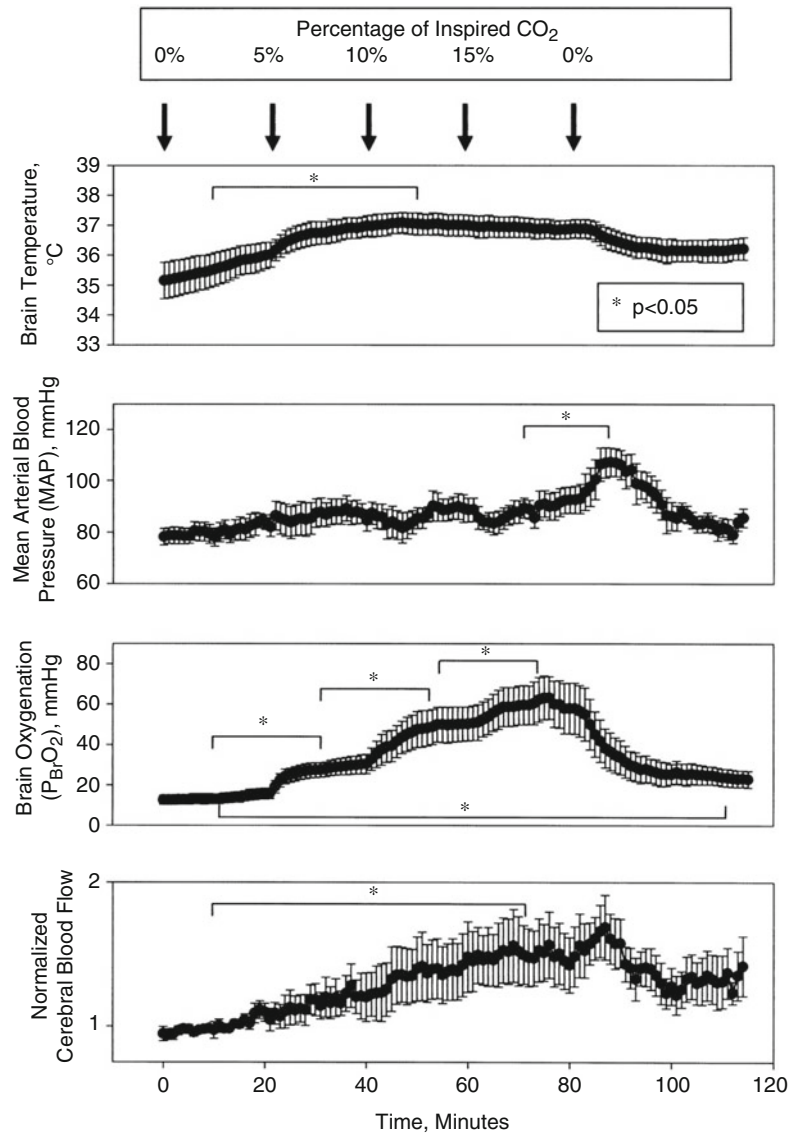
way constriction means hypercapnia has been variably reported as either increasing (Rodarte and Hyatt 1973) or decreasing (van den Elshout et al. 1991) airways resistance; indeed, the overall effect may be little *net* change. Hypercapnic acidosis increases parenchymal lung compliance, the reasons for which may be increased surfactant secretion, or more effective surface tension-lowering properties under acidic conditions (Wildeboer-Venema 1980).

CO_2 can affect regional lung perfusion either as part of a primary change in ventilation or a primary change in perfusion. An example is the phenomenon of hypocapnic bronchoconstriction that occurs following acute regional pulmonary artery occlusions (Swenson et al. 1961, 1995). The effects of hypercapnia on pulmonary vascular resistance appear to depend on whether there is preexisting pulmonary hypertension. Data from a porcine model of pulmonary hypertension induced by chronic hypoxia suggests that the effect of hypercapnia on pulmonary vascular resistance is not amplified by preexisting pulmonary hypertension (Lee et al. 2003). This is reassuring if newborns with primary pulmonary hypertension are to be managed with a strategy of permissive hypercapnia. Direct administration of CO_2 can improve matching of ventilation and perfusion and thus improve oxygenation in disease (Keenan et al. 1990) and health (Domino et al. 1993; Hare et al. 2003; Swenson et al. 1994). In ARDS, the increased shunt observed with permissive hypercapnia appears to be due to atelectasis resulting from low tidal volumes without a recruitment strategy – and not as a direct effect of hypercapnia (Feihl et al. 2000).

26.2.2 Central Nervous System

Hypercapnia potently stimulates ventilation with even mild elevations above normal levels (e.g., end-tidal PCO_2 +8 mmHg) and results in compensatory renal bicarbonate generation over 24–48 h (Crosby et al. 2003). The increased perfusion associated with hypercapnic acidosis results in greater cerebral oxygen delivery, an effect potentiated by a rightward shift of the Hb- O_2 dissociation curve (see below), increasing availability of the local PaO_2 (Hare et al. 2003) (Fig. 26.1).

Fig. 26.1 Brain tissue O_2 tension, as well as cerebral perfusion, is progressively increased with increases in inspired CO_2 concentration (Reproduced with permission, Hare et al. (2003))



26.2.3 Cardiovascular System

Hypercapnic acidosis has complex opposing effects on the cardiovascular system. Activation of the sympathoadrenal axis results in indirect effects including increases in preload, heart rate, and myocardial contractility, as well as reduced afterload. These indirect effects are in part offset by direct reduction of cardiac and vascular smooth muscle contractility (Tang et al. 1991), with a net increase in cardiac output (Cullen and Eger 1974).

The complex interaction of hypoxic pulmonary vasoconstriction, intrapulmonary shunt, and elevated cardiac output ultimately results

in increased global and regional O_2 delivery (Cardenas et al. 1996). Tissue oxygen delivery is enhanced by hypercapnic acidosis (above) increasing subcutaneous and intestinal O_2 tension (Ratnaraj et al. 2004) and presumably in multiple other systemic tissues also.

26.3 Insights from Laboratory Studies

The effects of hypercapnia and acidosis in relevant preclinical models of lung and systemic organ injury are increasingly well understood.

A clear understanding of these effects – both beneficial and deleterious – should guide the rational use of hypercapnia in the clinical setting. In addition, such knowledge will provide insights into the potential contribution of hypercapnia to the beneficial effects of low tidal volume ventilation.

26.3.1 Pulmonary

Hypercapnic acidosis has been demonstrated to have independent beneficial effects in the setting of acute lung injury following ischemia-reperfusion, free radical injury, mechanical stretch, and hypoxia-induced pulmonary hypertension. Hypercapnic acidosis, generated by increasing the inspired CO₂, directly attenuates acute lung injury induced by ischemia-reperfusion (Shibata et al. 1998; Laffey et al. 2000a) and free radical mechanisms (Shibata et al. 1998). In contrast, hypocapnic alkalosis *worsens* reperfusion-induced lung injury (Laffey et al. 2000b; Laffey and Kavanagh 2002). In in vivo pulmonary ischemia-reperfusion, hypercapnic acidosis lessened protein leak and preserved lung mechanics. These effects then resulted in subsequent improvement in oxygenation with hypercapnic acidosis as compared to normocapnia (Laffey et al. 2000c). Hypercapnic acidosis has also been demonstrated to attenuate lung injury following mesenteric ischemia-reperfusion (Laffey et al. 2003a), which occurred despite the associated elevations in pulmonary arterial pressures.

Hypercapnic acidosis has benefit in chronic hypoxia-induced pulmonary hypertension in newborn rats (Kantores et al. 2006). In this model, animals were randomized (at birth) to 0, 5.5, or 10 % added CO₂ and were also randomized to either normoxia (21 % O₂) or moderate hypoxia (13 % O₂). Pulmonary hypertension (*characterized by increased pulmonary arterial resistance, right ventricular hypertrophy, right ventricular dysfunction, pulmonary artery smooth muscle hypertrophy*) was reliably induced by chronic hypoxia but was attenuated by inspired CO₂. Indeed, a dose response was seen between level of inspired CO₂ and the inhibition of pulmonary vas-

cular remodeling, while both 5 and 10 % inspired CO₂ normalized right ventricular dysfunction. Finally, exposure to 10 % CO₂ also reduced oxidative lung injury and prevented upregulation of endothelin-1, a critical mediator of pulmonary vascular remodeling (Kantores et al. 2006).

The effects of hypercapnic acidosis in stretch-induced lung injury are more complex. Two key studies have demonstrated that the addition of inspired CO₂ attenuated Ventilator-induced Lung Injury (VILI) in the ex vivo (Broccard et al. 2001) and in vivo (Sinclair et al. 2002) rabbit lung. However, the benefits of supplemental CO₂ are not as pronounced in models where tidal volumes used are comparable to clinical values (i.e., in terms of mL/kg of body weight). For example, one model used a clinically relevant high tidal volume strategy (12 mL/kg) and demonstrated that in this context, hypocapnia was potentially deleterious and hypercapnic acidosis somewhat protective (Laffey et al. 2003b). In contrast, in an atelectasis-prone model of lung injury, which may in part reflect neonatal respiratory distress syndrome, supplemental CO₂ did not lessen the injury (Rai et al. 2004). Furthermore, when hypercapnia was induced by reducing the respiratory rate (i.e., not by reducing the tidal volume or by adding CO₂ to the inspired gas), there was evidence of harm (Billert et al. 2003). Thus the benefits of hypercapnia appear to depend on the severity of lung stretch, with hypercapnia more protective in the setting of more severe stretch. The means of producing the hypercapnia also appears to be important, with inspired CO₂ being protective, while hypercapnia produced simply by reducing respiratory rate is potentially deleterious.

In addition, hypercapnia may impair the healing process following lung injury. In this regard, Doerr et al. reported that, while hypercapnia minimized the adverse effects of high-volume ventilation on vascular barrier function, it also impaired the ability of lung cells to repair following high-stretch injury (Doerr et al. 2005). Hypercapnia – both in the presence (O'Toole et al. 2009) and absence of acidosis (O'Toole et al. 2009; Nichol et al. 2009) – inhibits healing of pulmonary epithelial wounds in vitro. The mechanisms underlying this inhibitory effect of

hypercapnia on wound healing appear to involve inhibition of the activity of nuclear factor kappa B (NF- κ B), a pivotal transcriptional activator in the setting of injury and repair (O'Toole et al. 2009).

Hypercapnia may also have a negative impact on diaphragmatic function, as it interferes with neuromuscular transmission and causes a reduction in cross-sectional area of type IIB fibers (Shiota et al. 2004). Whether this interference with neuromuscular transmission translates into an important clinical effect remains to be proven. In fact permissive hypercapnia in one study was shown to augment weaning from mechanical ventilation (Mariani et al. 1999).

The potential for hypercapnia to impair the immune system response to live bacterial sepsis (Laffey et al. 2004a; Swenson 2004) is of concern given that lung injury or ARDS commonly develops in the context of severe sepsis (Dahlem et al. 2003). Consequently, determination of the effects of hypercapnia and acidosis in this setting has been the focus of much recent work. When endotoxin – the toxin produced by gram-negative bacteria – is administered by the intratracheal route, hypercapnic acidosis delivered *via* inspired CO₂ is protective (Laffey et al. 2004b). In contrast, hypercapnia produced by reduced respiratory rate appears to worsen the severity of lung injury produced by systemic endotoxemia (Lang et al. 2005). Of perhaps greater relevance to the clinical setting, more recent work has demonstrated beneficial effects in animal models of severe acute pneumonia (Ni Chonghaile et al. 2008a) as well as established severe pneumonia (Ni Chonghaile et al. 2008b). However, hypercapnic acidosis did not modulate the severity of less severe pneumonia-induced lung injury (O'Croinin et al. 2005). Of more concern, sustained environmental hypercapnia worsened the severity of lung injury induced by prolonged bacterial pneumonia (O'Croinin et al. 2008). To summarize, the effects of hypercapnic acidosis in models of pneumonia depend on the severity of pneumonia and the methods by which hypercapnia is attained.

The effects of hypercapnia and acidosis in the setting of systemic sepsis are increasingly well understood. Hypercapnic acidosis attenuated shock and acute lung injury cecal ligation and

puncture (Costello et al. 2009). These protective effects were seen in both the early phases and in the setting of prolonged systemic sepsis (Costello et al. 2009). Interestingly, buffering of the hypercapnic acidosis attenuated its protective effects on the lung, while preserving its beneficial hemodynamic effects (Higgins et al. 2009). These studies provide some reassurance regarding the safety of permissive hypercapnia in the setting of sepsis but there is also evidence of the potential for hypercapnic acidosis to have a negative impact in sepsis. In summary, the effects of hypercapnia and acidosis appear to depend on the severity and duration of the septic insult, and also to some extent on the primary site of sepsis.

26.3.2 Cardiovascular

The benefits of hypercapnic acidosis in myocardial ischemia-reperfusion are well characterized (Nomura et al. 1994). However, the associated protection may be a function of the acidosis *per se* (as opposed to the elevated PCO₂) since reduction in *in vivo* myocardial infarct size occurs whether acidosis results from elevated CO₂ or from metabolic causes (Kitakaze et al. 1988, 1997; Preckel et al. 1998). However, increased coronary blood flow is also seen with hypercapnic acidosis (Nomura et al. 1994; Arellano et al. 1999), and this may confer additional benefits beyond those observed with metabolic acidosis. However, on the negative side, the presence of hypercapnic acidosis may reduce the likelihood of successful resuscitation following experimental ventricular fibrillation (von Planta et al. 1991).

26.3.3 Neurologic

While an increasing FiCO₂ can improve cerebral oxygenation in a dose-dependent manner in anesthetized rats (Hare et al. 2003), the effect of CO₂ in hypoxic-ischemic brain injury models is dose dependent. Hypercapnic acidosis does protect against hypoxic-ischemic injury in the immature brain in porcine (Barth et al. 1998; Rehncrona et al. 1989) and rodent (Vannucci

et al. 1995, 1997) models. However, the most benefit occurred in the mild to moderate range of hypercapnia (PaCO_2 40–55 mmHg), as compared to higher levels of PaCO_2 (e.g., >70 mmHg) (Vannucci et al. 1995). Indeed, even higher levels of PaCO_2 that are not generally seen in the clinical setting may be detrimental to the immature brain (Vannucci et al. 2001). Reasons for protective effects of hypercapnia in hypoxic brain injury include free radical inhibition (Barth et al. 1998; Rehncrona et al. 1989), attenuation of neuronal apoptosis, and reduction in the CNS levels of glutamate (a neurotransmitter that can cause excitotoxicity) (Vannucci et al. 1997).

Hypercapnia has the potential to contribute to retinopathy of prematurity since it has been shown experimentally to produce preretinal neovascularization similar to that seen in oxygen-induced retinopathy in a neonatal rat model (Holmes et al. 1998). This is of obvious concern in the clinical setting of neonatal respiratory failure.

26.3.4 Others

The response of cells to hypercapnia and hypoxia unsurprisingly depends on their origin. For instance, renal tubular cells undergo apoptosis in response to hypoxia/hypercapnia (Hotter et al. 2004). In contrast, isolated hepatocytes exposed to anoxia (Bonventre and Cheung 1985) and chemical hypoxia (Gores et al. 1989) show improved survival under acidotic conditions which may be an adaptive phenomenon against hypoxic-ischemic stress.

26.4 Cellular and Molecular Effects of Hypercapnia

To anticipate potential pitfalls of permissive hypercapnia and to complete translational research from bench to bedside, it will eventually be important to have a basic understanding of the cellular and biochemical effects of hypercapnia. In keeping with the trend towards individualized medicine, increasing appreciation of the underlying molecular mechanisms may allow the

clinical practitioner to ultimately identify those situations in which permissive hypercapnia may be beneficial. Knowledge of molecular mechanisms of hypercapnia will also help identify the circumstances in which it may cause harm.

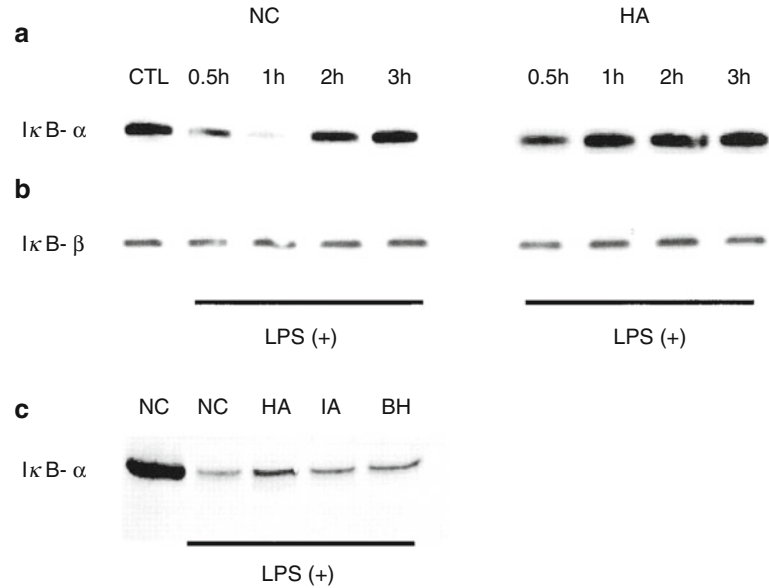
26.4.1 Acidosis vs. Hypercapnia

The protective effects of hypercapnic acidosis appear to be a function of the acidosis generated as opposed to hypercapnia per se (Laffey et al. 2000a; Higgins et al. 2009; Lang et al. 2000). The beneficial effects of hypercapnic acidosis in ischemia-reperfusion in an isolated lung model were ablated if the pH was buffered towards normal (Laffey et al. 2000a). Furthermore, buffering of the hypercapnic acidosis abolished the protective effects on the lung in the setting of systemic sepsis (Higgins et al. 2009). Metabolic acidosis demonstrates protective effects in many models of organ injury including the myocardium (Kitakaze et al. 1988, 1997; Preckel et al. 1998), liver (Bonventre and Cheung 1985), and kidney (Bonventre and Cheung 1985). In the latter, isolated renal cortical tubules exposed to anoxia have better conserved ATP status where reoxygenation occurs in an acidotic (vs. alkalotic) environment (Bonventre and Cheung 1985). However, the inhibition of wound healing by hypercapnic acidosis in experimental models be it cell culture (O'Toole et al. 2009) or in an ex vivo model (Caples et al. 2009) would appear to be independent of buffering.

26.4.2 Regulation of Gene Expression

Hypercapnic acidosis affects a key transcriptional factor, nuclear factor kappa B (NF- κ B), which is an important regulator of the expression of multiple genes that play a central role in inflammation and repair. Hypercapnic acidosis inhibits endotoxin-induced NF- κ B activation and DNA binding in pulmonary endothelial cells by decreasing I κ B- α degradation (Fig. 26.2) (Takeshita et al. 2003). Endothelial production of intercellular adhesion molecule ICAM-1 and interleukin-8

Fig. 26.2 Hypercapnia suppresses the degradation of I κ B- α (Panel **a**) but not I κ B- β (Panel **b**) following exposure to lipopolysaccharide, thereby inhibiting the nuclear translocation of NF κ -B and downstream cytokine production. The effects of isocapnic acidosis and buffered hypercapnia (Panel **c**) on I κ B- α degradation were intermediate between normocapnic control and hypercapnic acidosis conditions. *Symbols: BH* buffered hypercapnia, *HA* hypercapnic acidosis, *IA* isocapnic acidosis, *LPS* lipopolysaccharide, *NC* normocapnia, *NF κ -B* nuclear factor kappa B (Reproduced with permission, Takeshita et al. (2003))



are downstream effects, reflecting suppression of NF- κ B activation by hypercapnic acidosis. While inhibition of NF- κ B can have anti-inflammatory effects, inhibition may also effect wound healing. Hypercapnic acidosis was shown to inhibit pulmonary wound healing *via* an NF- κ B-dependent mechanism (O'Toole et al. 2009).

26.4.3 Attenuation of Neutrophil Activity and Cytokine Levels

Another key component of the inflammatory response which is inhibited by hypercapnic acidosis is neutrophil function. Hypercapnic acidosis interferes with neutrophil intracellular pH regulation (Hackam et al. 1996), and this is associated with attenuation of important neutrophil functions such as chemotaxis (Demaurex et al. 1996) and release of interleukin-8 (IL-8) following LPS stimulation (Coakley et al. 2002). These effects are also seen in vivo where lung neutrophil recruitment is inhibited during ventilator-induced (Sinclair et al. 2002) and endotoxin-induced (Laffey et al. 2004b) lung injury. Hypercapnic acidosis has been demonstrated to reduce neutrophil phagocytic activity (O'Croinin et al. 2008). Finally, hypercapnic acidosis inhibits other proximal inflammatory

responses, such as production of TNF- α following in vivo pulmonary ischemia-reperfusion (Laffey et al. 2000c) as well as release of TNF- α and IL-1, release from stimulated in vitro macrophages (West et al. 1996).

26.4.4 Modulation of Free Radical Biology

The potential for hypercapnic acidosis to promote nitration of lung tissue in vivo appears to depend on the particular injury process in question. One potential problem with hypercapnic acidosis is its potential to augment tissue nitration by peroxynitrite, a potent free radical as demonstrated when buffered hypercapnia promotes the formation of nitration products from peroxynitrite in vitro (Lang et al. 2000; Zhu et al. 2004). Hypercapnic acidosis increases nitration following endotoxin exposure (Laffey et al. 2004b; Lang et al. 2000, 2005) but decreases it following pulmonary ischemia-reperfusion (Laffey et al. 2000c).

In contrast, hypercapnic acidosis appears to reduce oxidant production and oxidant-mediated tissue injury. Enzymes which produce oxidizing free radicals function optimally at physiological pH. Neutrophil activity is regulated in part by ambient CO₂ levels with hypercapnia

inhibiting – and hypocapnia increasing – the production of oxygen-derived free radicals (Coakley et al. 2002). Superoxide synthesis by stimulated neutrophils in vitro is decreased at acidic pH (Leblebicioglu et al. 1996). In lung ischemia-reperfusion models, hypercapnic acidosis reduces free radical tissue injury (Laffey et al. 2000c) and inhibits the production of higher oxides of NO following both ventilator-induced (Broccard et al. 2001) and endotoxin-induced (Laffey et al. 2004b) lung injury. In the brain, glutathione depletion and lipid peroxidation – reflecting free radical activity– and resultant tissue damage are attenuated by hypercapnic acidosis (Barth et al. 1998).

26.5 Role of Permissive Hypercapnia in Clinical Settings

Once ventilator-induced lung injury has occurred, there are currently no available therapies to reverse it; thus, the focus in recent years has been on minimizing ventilator-induced lung injury. Since the recognition that end-inspiratory distension may be a prime determinant of lung injury (Dreyfuss and Saumon 1998), avoidance of high tidal volumes has become a focus of management. While increasing respiratory rate can control the PaCO₂, the mechanical properties of the injured lung are a limiting factor since they determine the time

necessary for inspiration and expiration. Thus permissive hypercapnia will occur using low tidal volumes, particularly as lung compliance is lowered. But is permissive hypercapnia beneficial – or even safe – in specific pediatric clinical scenarios?

26.5.1 Neonatal Respiratory Distress Syndrome

Mariani et al. reported beneficial effects of permissive hypercapnia in 49 infants with neonatal respiratory distress syndrome in the first randomized controlled trial of permissive hypercapnia (Mariani et al. 1999). Preterm infants randomized to permissive hypercapnia received lower tidal volumes, and they required fewer days of assisted ventilation compared with children (mean 2.5 vs. 9.5 days) (Fig. 26.3). No obvious adverse effects were seen, but the study was not powered adequately to draw conclusions regarding safety. However, the use of postnatal steroids, total duration of oxygen supplementation, and incidence of air leaks, reintubations, and chronic lung disease did not differ between those randomized to permissive hypercapnia or conventional ventilation (Fig. 26.3).

A multicenter trial by the National Institutes of Child Health and Development Neonatal Network randomized extremely low-birth-weight infants ventilated before 12 h of life to

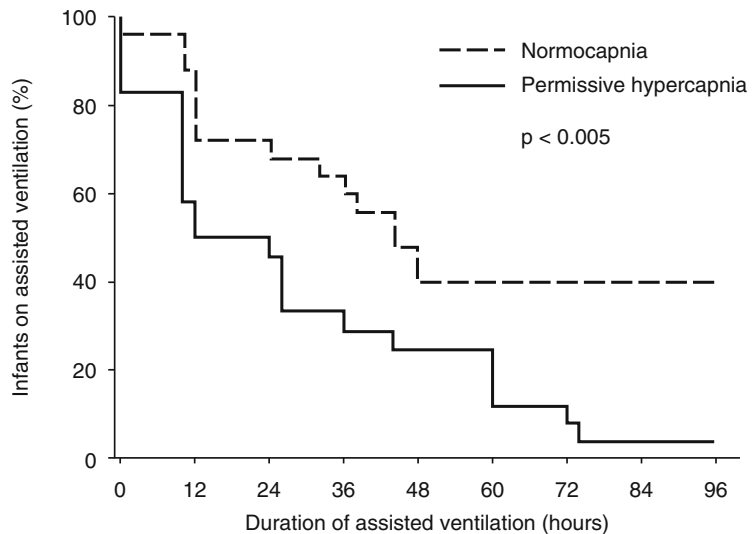


Fig. 26.3 Duration of mechanical ventilation in neonates with respiratory failure randomized to conventional therapy or permissive hypercapnia (Reproduced with permission, Mariani et al. (1999))

normocapnia or permissive hypercapnia as well – in a factorial design – to dexamethasone vs. placebo (Carlo et al. 2002). The study, however, was stopped early after enrolment of 220 patients because of an unexpected increased incidence of bowel perforation in infants receiving early dexamethasone. Nonetheless, there was a trend towards a lower incidence of death and chronic lung disease with permissive hypercapnia, and only 1 % of permissive hypercapnia group patients required mechanical ventilation at 36 weeks, compared to 16 % in the control group. No adverse effects were specifically associated with permissive hypercapnia; in fact, infants receiving permissive hypercapnia appeared to have a lower incidence of severe intraventricular hemorrhages (20 % vs. 26 %) (Carlo et al. 2002).

The most recent trial in 2006 was again stopped prematurely after enrolment of only 40 patients when the permissive hypercapnia group showed nonsignificant trends towards increased mortality and poorer neurological outcome (Thome et al. 2006). Thus what little evidence is available in this particular setting is conflicting, but the uncertainty highlights the need for further understanding of the mechanisms and effects of hypercapnia before additional large randomized controlled clinical trials are undertaken.

26.5.2 Persistent Pulmonary Hypertension of the Newborn (PPHN)

The poor neurological outcome associated with PPHN can be explained in part by a traditional approach of using hyperventilation (and targeted hypocapnia) to lower pulmonary arterial pressure (Drummond et al. 1981; Ferrara et al. 1984; Leavitt et al. 1987). In one small series of 15 infants where treatment focused on minimizing barotrauma (allowing PaCO₂ as high as 60 mmHg), all children survived, and only a single patient developed chronic lung disease (Wung et al. 1985). In another series of 34 infants with severe PPHN managed with permissive hypercapnia, Marron et al. reported 100 % survival, with good neurologic outcome (Marron et al. 1992).

26.5.3 Congenital Diaphragmatic Hernia

Ventilation strategies which involve achieving systemic alkalization through hyperventilation may result in poor long-term outcomes. Thus permissive hypercapnia has begun to play a more prominent role in the management of congenital diaphragmatic hernia (Bohn 2002). In a recent retrospective analysis, Bagolan et al. reported that strategies allowing permissive hypercapnia to develop were beneficial (Bagolan et al. 2004). Increased survival and reduced barotrauma and morbidity were associated with the use of permissive hypercapnia. However, the use of high-frequency oscillation provides a mechanism for controlling (i.e., lowering) PaCO₂ without the use of high tidal volumes. In this setting, it is not clear whether hypocapnia or high tidal volume (or both) are responsible for adverse pulmonary (or CNS) outcome.

26.5.4 Congenital Heart Disease

Low cerebral blood flow has been associated with periventricular leukomalacia and adverse neurologic outcome in neonates with severe congenital heart defects (Licht et al. 2004). Thus preventing reduced cerebral perfusion – or augmenting it – would be desirable. Licht et al. showed significant deficits in cerebral blood flow that were reversed when CO₂ was administered in small series of 25 infants (Licht et al. 2004). Also, the addition of inspired CO₂ increased cerebral oxygenation and mean arterial pressure compared with reducing FiO₂ in hypoplastic left heart syndrome (Tabbutt et al. 2001) and following cavopulmonary connection (Ramamoorthy et al. 2002), respectively.

Following cavopulmonary connection, traditional management has focused on avoiding hypercapnia because of the fear that hypercapnia would increase pulmonary vascular resistance and reduce systemic oxygenation. Recent evidence has demonstrated that hypoventilation-induced hypercapnia actually increases pulmonary perfusion primarily through augmentation of systemic blood flow and a reduction of systemic vascular index (Bradley et al. 2003). In addition, allowing

PaCO₂ to return to 40 mmHg following hypercapnia decreases pulmonary blood flow and systemic oxygenation following cavopulmonary connection (Hoskote et al. 2004).

26.5.5 Acute Severe Asthma

Darioli and Perret were the first to describe avoidance of lung injury through lowering tidal volume (and permitting hypercapnia) (Darioli and Perret 1984); in their series, they described mechanically ventilated patients with status asthmaticus, in whom there were no deaths in 26 patients. In status asthmaticus, plateau pressure and tidal volume are reduced and expiratory time increased in order to lower end-inspiratory lung volume and (potentially lethal) barotrauma. Such an approach can result in significant levels of hypercapnia which is usually well tolerated, although life-threatening acidosis has been managed successfully with extracorporeal arteriovenous carbon dioxide removal (Conrad et al. 2007).

26.5.6 Acute Respiratory Distress Syndrome

Trials in adult patients with ARDS have demonstrated the importance of avoiding high tidal volumes or plateau pressures in order to improve survival; such approaches result in some degree of permissive hypercapnia (The Acute Respiratory Distress Syndrome Network 2000; Amato et al. 1995, 1998). While reduced lung stretch no doubt played the major part in achieving lower mortality, the possibility that permissive hypercapnia independently contributed was explored by Kregnow et al. (2006). Using multivariate analysis, and controlling for other comorbidities and severity of lung injury, it appeared that permissive hypercapnia reduced mortality in patients who received higher tidal volumes, but not in those who received lower tidal volumes (Kregnow et al. 2006). This constitutes evidence that in humans, hypercapnia can

protect against ventilator-induced lung injury, and represents the first clinical data supporting a beneficial effect of hypercapnia in ALI/ARDS patients.

26.6 Limitations and Contraindications of Permissive Hypercapnia

In certain clinical contexts, the potential for hypercapnia to exert detrimental effects needs to be carefully considered since hypercapnia and acidosis exert important biological effects.

26.6.1 Permissive Hypercapnia and the Immature Brain

Considerable fluctuations in cerebral blood flow can result from altered CO₂ levels in very low-birth-weight infants; this can predispose to intraventricular hemorrhage in the immature brain (Skouteli et al. 1988; Szymonowicz et al. 1984; Wallin et al. 1990). Kaiser et al. demonstrated that in such infants, hypercapnia was associated with a progressive loss of cerebral autoregulation (Kaiser et al. 2005). By allowing modest rather than severe hypercapnia (or hypocapnia) (Skouteli et al. 1988) and avoiding fluctuations in blood pressure and sudden increases in PCO₂, any increased risk of intraventricular hemorrhage should be minimized.

In addition, hypercapnia may indirectly protect the developing brain by avoiding accidental hypocapnia. Hypocapnia has multiple deleterious effects on the immature brain (Laffey and Kavanagh 2002). Preterm infants exposed to severe hypocapnia (PaCO₂ <15 mmHg), even for a short duration, can develop lasting neurologic abnormalities (Greisen et al. 1987), possibly due to reduced cerebral perfusion. In addition, abrupt termination of hyperventilation can result in reactive cerebral hyperemia and precipitate intracranial hemorrhage (Gleason et al. 1989). As already discussed, experimental evidence exists that hypercapnia may directly protect the

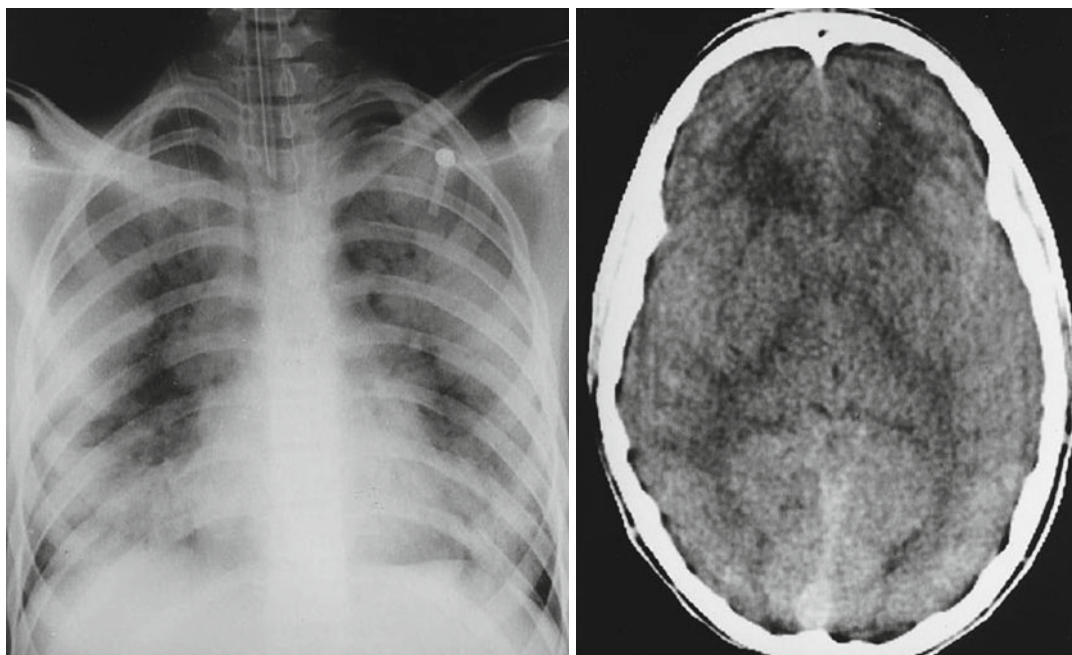


Fig. 26.4 A chest radiograph and brain CT scan of a child with both ARDS and cerebral edema, illustrating the “trade-off” involved in instituting permissive hypercapnia

in order to protect against ventilator-associated lung injury (Reproduced with permission, Tasker and Peters (1998))

immature brain from hypoxic-ischemic-induced injury (Vannucci et al. 1995, 1997).

26.6.2 Intracranial Pressure Regulation

Where intracranial compliance is diminished, increases in cerebral blood flow are detrimental (Tasker and Peters 1998), and a key fear regarding permissive hypercapnia is the potential for hypercapnia-induced increases in cerebral blood flow to elevate intracranial pressure above a critical threshold. However, clinical conditions involving intracranial hypertension constitute a relative rather than an absolute contraindication to permissive hypercapnia. The use of an intracranial pressure monitor (or a jugular venous oximetry catheter) should be considered to aid the titration of permissive hypercapnia in cases of suspected raised intracranial pressure. Indeed the successful use

of such an approach has been described in the management of a child suffering from meningococcal septicemia complicated by both significantly elevated intracranial pressure and severe acute lung injury (Fig. 26.4) (Tasker and Peters 1998).

26.6.3 Pulmonary Vascular Resistance

Laboratory studies demonstrate that hypercapnic acidosis may attenuate the development of hypoxia-induced pulmonary hypertension in newborn rodents (Kantores et al. 2006). However, clinical conditions predisposing to pulmonary hypertension should also be considered when using permitting hypercapnia; here, titrating the PaCO_2 against the estimated pulmonary vascular resistance might be reasonable. Thus, in this clinical scenario, the use of a pulmonary artery catheter or echocardiography may be useful.

26.6.4 Buffering Hypercapnia

The requirement to consider the effects of buffering hypercapnic acidosis is emphasized by the fact that both hypercapnia and acidosis may exert discrete biologic effects. Buffering of the acidosis induced by hypercapnia remains a frequent controversy in clinical practice. In fact, buffering with sodium bicarbonate was common in the ARDS Network study (2000). As discussed earlier, there is evidence that the protective effects of hypercapnic acidosis in ARDS may be a function of the acidosis rather than CO_2 per se (Laffey et al. 2000a; Higgins et al. 2009). Furthermore, the deleterious effect of hypercapnic acidosis on pulmonary epithelial wound healing is not ablated when the hypercapnia is buffered (O'Toole et al. 2009; Nichol et al. 2009). However, Caples et al. have shown buffered hypercapnia to have protective effects both in ventilator-induced lung injured rat lungs and in an in vivo model of cell membrane injury (Caples et al. 2009). Therefore, buffering may simply ablate the protective effects while only having limited effects on the deleterious effects of hypercapnic acidosis.

Where alveolar ventilation is limited, such as ARDS (Sun et al. 1987), bicarbonate may further raise PaCO_2 since effectiveness of bicarbonate infusion as a buffer is dependent on the ability to excrete CO_2 . The ability of bicarbonate to correct arterial pH comes at the cost of worsening intracellular acidosis (Shapiro et al. 1989), because when bicarbonate reacts with metabolic acids, the CO_2 produced diffuses readily across cell membranes, whereas the bicarbonate does not (Goldsmith et al. 1997). In addition, bicarbonate increases the burden of CO_2 that needs to be eliminated, in a context where such elimination is diminished either by the underlying disease or by the adoption of a low tidal volume strategy.

26.7 Summary and Conclusions

Non-injurious ventilator strategies involving permissive hypercapnia are widely utilized in the critically ill neonate and child, primarily to

reduce volutrauma. The potential for hypercapnia to exert independent beneficial effects has been shown in numerous experimental studies. Arising from this body of experimental work is the possibility that hypercapnia might be induced for therapeutic effect. However, concerns remain regarding the potential for hypercapnia and/or acidosis to cause harm. Thus, the clinician needs to balance the risks and benefits of the overall context, with as yet, incomplete information.

In the future, a clearer understanding of the effects and mechanisms of action of hypercapnia will be used to determine its safety, utility, and role in specific situations. However, this knowledge is as yet incomplete, and except for obvious contraindications, the precise contribution of hypercapnia to the management of any given patient remains unclear.

Essentials to Remember

- Protective ventilatory strategies that reduce lung stretch require tolerance of “permissive” hypercapnia and have demonstrated benefit in the critically ill neonate and child.
- Hypercapnia is a potent biologic agent, and there is increasing evidence from laboratory studies that hypercapnia may directly attenuate lung and systemic organ injury.
- The potential for hypercapnia to exert deleterious physiologic effects, particularly where intracranial compliance is reduced or where increases in pulmonary vascular resistance may be deleterious, must be considered.
- There is no clinical evidence to support the clinical practice of buffering hypercapnic acidosis with bicarbonate.

When using ventilation strategies involving permissive hypercapnia, the clinician must continue to decide for each specific patient what the appropriate trade-off is between the benefits of avoiding high tidal volumes and the cost – and benefits – of the associated hypercapnia.

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Permissive Hypercapnia in Neonates: Specific Experience and Limitations

27

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“Thirty years of physiologic, clinical, and experimental knowledge converge on a common point: mechanical ventilation settings should obey a simple and old concept: treat the lung gently”. Luciano Gattinoni, Crit Care Med, 2003

“Perhaps the only consensus about mechanical ventilation of infants is that, all else being equal, avoidance of mechanical ventilation is the best way to avoid lung injury”. Alan Jobe, J Pediatr 2006

Educational Aims

- To examine the physiologic rationale behind permissive hypercapnia, the experimental and clinical data assessing its potential use in neonates
- To assess the effectiveness and safety of early nasal CPAP and permissive hypercapnia in non-ventilated preterm infants neonates
- To review the role of permissive hypercapnia as a lung-protective ventilatory strategy in preterm neonates
- To consider the risks of permissive hypercapnia in preterm infants

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27.1 Introduction

Two decades ago, a consensus of experts on mechanical ventilation (MV) indicated that one of the potential strategies to reduce lung injury was to modify blood-gas targets to accept a higher-than-normal PaCO₂ (Slutsky 1993). This approach to ventilator support has been called permissive hypercapnia, also termed controlled mechanical hypoventilation. In the past, many clinicians aimed to achieve PaCO₂ levels of 40 mmHg or less in ventilated neonates. Experimental and clinical researches during the last two decades indicate that slightly higher PaCO₂ levels may allow a reduction in ventilatory support and may reduce the risk for lung injury.

Ventilator-supported infants develop a form of chronic lung disease called bronchopulmonary dysplasia (BPD). Even though the pathophysiology of the “new BPD” (Jobe 1999) differs from the “classical” one described more than 40 years ago by Northway et al. (1967), there is consensus among neonatologists that it is important to avoid ventilator-induced lung injury in neonates and its long-term consequences by improving ventilatory strategies. Permissive hypercapnia is one of the ventilatory strategies that is likely to help avoid complications due to mechanical ventilation.

When applying a novel approach, we should consider both the potential benefits as well as the

Table 27.1 Potential benefits and risks of permissive hypercapnia in neonates

Potential benefits	Potential risks
Decrease lung injury	Cerebral vasodilation/loss of cerebral auto regulation/ intraventricular hemorrhage
Neuroprotection in hypoxia-ischemia	Increase pulmonary vascular resistance
Reduction of adverse effects of hypocapnia including periventricular leukomalacia and cerebral palsy	Decrease myocardial contractility
Improved cardiac output	Increase retinopathy of prematurity
Decrease duration of assisted ventilation	

possible risks. For permissive hypercapnia, these are summarized in Table 27.1.

We will review the physiologic rationale behind permissive hypercapnia, the experimental and clinical data assessing its potential use in neonates, and the trials that have evaluated this strategy in this vulnerable population.

27.2 Physiologic Rationale

27.2.1 Potential Advantages of Hypercapnia and Hypercapnic Acidosis

A ventilator management strategy that permits hypercapnia has several physiologic effects on gas exchange, cardiac output, and respiratory drive that may be beneficial. The increase in alveolar CO_2 that occurs during permissive hypercapnia increases CO_2 elimination for the same minute ventilation. This is because CO_2 elimination is governed by the following equation:

$$K \times V\text{CO}_2 = \text{PACO}_2 \times VA$$

In this equation, K is a constant, $V\text{CO}_2$ is CO_2 elimination, PACO_2 is alveolar CO_2 , and VA is alveolar ventilation. If the PACO_2 is allowed to rise and alveolar ventilation is kept constant, CO_2 elimination will increase. Therefore, a clinician can use lower tidal volumes and lower peak inspiratory pressures (decreasing alveolar ventilation) and allow the CO_2 to rise, yet maintain effective CO_2 removal. The hyperbolic relationship between PaCO_2 and minute ventilation permits effective CO_2 removal at a

lower-than-expected amount of alveolar ventilation (Boydton and Hammond 1994). Thus, for example, if alveolar ventilation decreases by half, PaCO_2 will increase twofold but the increase in alveolar CO_2 tends to maintain a constant CO_2 elimination.

Aside from increasing the efficiency of CO_2 removal, hypercapnia (achieved with inspired CO_2 in animal studies) can improve ventilation-perfusion matching in the lung (Swenson et al. 1994; Brogan et al. 2004; Sinclair et al. 2006). In addition, hypercapnic acidosis permits more unloading of oxygen to the tissues due to the rightward shift of the oxygen dissociation curve (Bohr effect). Another physiologic advantage is stabilization (or increase) in respiratory drive, resulting in less apnea (Kondo et al. 2000) that can facilitate weaning an infant off the ventilator (Mariani et al. 1999; Søvik and Lossius 2004). Permissive hypercapnia also has beneficial effects related to cardiac function. Hypercapnia causes intracellular acidosis in the cardiac myocyte because of the high permeability to CO_2 (Laffey and Kavanagh 1999). In animals and humans, both therapeutic hypercapnia and permissive hypercapnia have been shown to decrease cardiac contractility but increase overall cardiac output (Walley et al. 1990; Weber et al. 2000). The increase in cardiac output is believed to be due to a fall in peripheral vascular resistance following hypercapnic acidosis (Cardenas et al. 1996). Furthermore, as tidal volume and peak inspiratory pressure are lowered, mean airway pressure decreases, which also may improve preload and cardiac output (Weiner et al. 1987; Gullberg et al. 1999, 2004).

27.2.2 Potential Disadvantages of Hypercapnic Acidosis

Possible negative effects of hypercapnia on gas exchange include a small reduction in alveolar O_2 concentration caused by the increased alveolar CO_2 . This can be overcome with slight increases in FiO_2 to increase alveolar oxygen concentration. Hypercapnic acidosis may also cause an increase in pulmonary vascular resistance in some infants although this has not been observed in clinical trials. In addition, while a higher $PaCO_2$ might be good, if the tidal volume is too low, the alveoli may collapse, resulting in right to left intrapulmonary shunting.

Hypercapnic acidosis also increases metabolic demand through an increase in work of breathing (Thome et al. 2006), but because oxygen delivery and tissue oxygenation is increased, this may not be clinically relevant. Hypercapnia may play a role in the development of retinopathy of prematurity (ROP) through retinal vessel vasodilatation, increased oxygenation, and subsequent formation of oxygen-derived free radicals (Holmes et al. 1998; Leduc et al. 2006). However, the randomized trials in neonates that tested for the presence of ROP or long-term visual outcomes reported no difference in the control versus the hypercapnia groups (Mariani et al. 1999; Thome et al. 2006; Carlo et al. 2002).

There is a particular concern in neonates of potential increased risk of IVH because of loss of cerebral autoregulation when exposed to high $PaCO_2$. However, this is not supported by the clinical trials (see later).

27.3 Experimental Research

27.3.1 Supportive Data for Hypercapnic Acidosis

Permissive hypercapnia allows a clinician to manage a ventilated patient with the intent of reducing lung injury resulting from volutrauma. Furthermore, the resulting hypercapnic acidosis itself may be advantageous to the injured lung and to other organs. It is important to distinguish

between permissive hypercapnia (the presence of hypercapnia in the setting of a ventilated patient being managed with low minute ventilation) and therapeutic hypercapnia (deliberate induction of hypercapnia by adding CO_2 to inspired gases, usually done experimentally) (Rotta and Steinhorn 2006). Each intervention produces hypercapnic acidosis, but therapeutic hypercapnia allows researchers to test experimentally the independent effects of hypercapnic acidosis. For example, in an in vivo rabbit model of high-tidal volume, ventilator-induced lung injury (25 mL/kg tidal volume in both experimental groups), therapeutic hypercapnia ($PaCO_2$ 80–100 mmHg versus 40 mmHg) attenuated various measures of lung injury (Sinclair et al. 2002). Similarly, in a rat model of endotoxin-induced lung injury in which lower volumes were used (4.5 mL/kg), therapeutic hypercapnia either before or after instillation of intratracheal endotoxin also reduced lung injury indices (Laffey et al. 2004). It is interesting to note that buffering hypercapnic acidosis to maintain “normal” pH may abrogate the protective effects of hypercapnic acidosis (Nichol et al. 2009). These studies demonstrate some of the potential benefits of hypercapnic acidosis per se in adult animal models in vivo. This is important because permissive hypercapnia, while decreasing the risk of lung injury due to mechanical reasons (lung stretch), also may be beneficial because of the additive effects of hypercapnia and of acidosis. Recent experimental research suggests that the beneficial effects of hypercapnic acidosis in the adult lung may translate to the preterm lung. Strand et al. (2003) showed that in preterm lambs with ventilator-induced lung injury, those exposed to high inspired PCO_2 had less lung injury by histopathology than control lambs. In newborn rats, hypercapnic acidosis had beneficial effects on pulmonary hypertension and vascular remodeling induced by chronic hypoxia (Kantores et al. 2006). Exposure to 10 % CO_2 attenuated increased oxidant stress induced by hypoxia, as quantified by 8-isoprostane content in the lung, and prevented upregulation of endothelin-1, a critical mediator of pulmonary vascular remodeling. Thus, CO_2 may have antioxidant properties

on the lung and consequent modulating effects on the endothelin pathway. Vannucci et al. (1995) studied an immature rat model of cerebral hypoxia-ischemia, finding that mild hypercapnia was associated with less severe brain damage than normocapnic animals.

Li et al. (2006) investigated the effect of hypercapnia on overall growth characteristics, lung structure, and global gene expression in lungs of newborn mice exposed to 8 or 12 % CO₂ for 2 weeks. Their research demonstrated a substantial number of genes with altered expression in mice exposed to 8 % CO₂ but not in those exposed to 12 % CO₂. Of particular interest was an increase in transcription of the genes encoding surfactant-associated protein A and B (Sftp-A and Sftp-B). These proteins, expressed in bronchial epithelial and type II alveolar cells, may contribute to host defense mechanisms in the lung. Overall growth (body weight), hemoglobin concentration, and lung alveolar development were normal in both the hypercapnia and control groups. Recent preliminary data demonstrate that hypercapnia may accelerate alveolar development and attenuate hyperoxia-induced fibrosis in neonatal mice (Ryu et al. 2010; Das et al. 2009). These data suggest that hypercapnic acidosis may enhance host defense mechanisms through altered gene expression and promote alveolar development in the developing lung.

One of the benefits of hypercapnic acidosis demonstrated by in vivo animal studies is reduced neutrophil influx into the lung and reduced inflammatory cytokine production (Sinclair et al. 2002; Laffey et al. 2000, 2004). Such anti-inflammatory effects of hypercapnic acidosis also have been studied in vitro using neutrophils and endothelial cells. Hypercapnia can affect various neutrophil functions such as chemotaxis by altering the ability of neutrophils to regulate intracellular pH (O’Croinin et al. 2005). Hypercapnic acidosis also can alter neutrophil adherence to pulmonary endothelial cells by decreasing endothelial expression of the adhesion molecule ICAM-1 and of the chemoattractant interleukin-8 (Takeshita et al. 2003). Furthermore, hypercapnic acidosis can decrease lipopolysaccharide (LPS)-stimulated secretion of the acute proinflammatory cytokine tumor necrosis

factor alpha in isolated rat macrophages (Lang et al. 2005a). The proposed mechanism of decreased expression of ICAM-1 and inflammatory cytokines appears to be related to decreased activation of nuclear factor kappa beta, a key early regulator of gene expression in the innate immune response (Watterberg et al. 1996). The ability of hypercapnic acidosis to modulate the innate immune response has important implications for lung development. Antenatal exposure to inflammation, such as chorioamnionitis, is a frequent cause of preterm birth and increases the risk of developing BPD (Watterberg et al. 1996; Jobe 2003). Furthermore, innate immune signaling can inhibit structural lung development in experimental animal models (Prince et al. 2005; Benjamin et al. 2007). Thus, hypercapnic acidosis also may be beneficial to the developing lung via its anti-inflammatory and immune-modulating capabilities. However, more experimental research is needed to determine how hypercapnic acidosis can be optimized to protect the preterm lung.

27.3.2 Neutral or Negative Data for Hypercapnic Acidosis

Even though most of the data indicate that hypercapnic acidosis is beneficial, some studies have reported neutral or negative results. Lang et al. (2005b) used intravenous LPS injection to mimic sepsis-related lung injury in adult rabbits and demonstrated that permissive hypercapnia contributed to lung injury via amplified oxidative injury. Other researchers have shown that hypercapnia may impair cell repair mechanisms after injury (Doerr et al. 2005) and induce injury to alveolar epithelial cells by potentiating tissue nitration (Lang et al. 2000). In an adult rabbit lung injury model using saline lavage to cause surfactant deficiency, therapeutic hypercapnia did not improve oxygenation or attenuate lung injury (edema, compliance, airway pressure, or cytokine production) after high-volume ventilation (12 mL/kg versus 5 mL/kg of tidal volume) (Rai et al. 2004). In eight adult patients with ARDS exposed to hypercapnia, there was a decrease in the Qp/Qs ratio, with deterioration in gas exchange (Feihl et al. 2000). Although a recent

preliminary report suggested that therapeutic hypercapnia (5.5 % inspired CO_2) could protect the neonatal rat lung from hyperoxic injury (Masood et al. 2009), other investigators who used higher CO_2 concentrations (8 % CO_2) did not report this benefit (Das et al. 2009). Hypercapnia has been associated with increased risk of impaired cerebral blood flow autoregulation and intracranial hemorrhage in neonates (Kaiser et al. 2005). Kaiser et al. (2005) have examined the effects of endotracheal tube suctioning on cerebral autoregulation at various levels of PaCO_2 . They found a relationship between acute PaCO_2 changes and cerebral blood flow. Marked hypercapnia can cause pressure-passive cerebral blood flow and increase risk of IVH. In another study, the same group suggested an association between severe hypercapnia in the first 72 h and IVH (Kaiser et al. 2006). It should be noted that the findings refer to fairly extreme degrees of hypercapnia, not what we typically feel to be appropriate target PaCO_2 levels, even in the context of permissive hypercapnia. In their study, the association of PaCO_2 and severe IVH involves very high levels (median 73.8, 25–75 % = 62.1, 84.7 for grade 3 IVH and median 73.9 25–75 % 65.4, 90.5 for grade 4 IVH). Even when a multivariate analysis was done, it is still not conclusive that there is a causative relationship, as opposed to an association of poor ventilation and severe IVH in the sickest babies. Furthermore, two large new clinical data suggest that severe hypocapnia and wide fluctuations in PaCO_2 in addition to hypercapnia were associated with increased risk of hemorrhage (Fabres et al. 2007; McKee et al. 2009) (see below). Nonetheless, there certainly is a plausible pathophysiologic mechanism and it is likely that very high PaCO_2 may be dangerous in the first 4 days of life. Other studies have shown that hypercapnic acidosis increases cerebral oxygen delivery (Hare et al. 2003) and that the CO_2 -induced alterations in cerebral blood flow appear to be reversible (Hino et al. 2000).

A recent retrospective study of 849 infants weighing 1,250 g or less revealed that severe hypocapnia, severe hypercapnia, and wide fluctuations in PaCO_2 were associated with increased risk of hemorrhage (Fabres et al. 2007). The OR for IVH was 1.97 (1.23–3.15) if the maximal

PaCO_2 was higher than 60 mmHg during the first 4 days of life and 2.51 (1.53–4.12) when the minimal PaCO_2 level was below 39 mmHg. Another retrospective study from the same group found that extreme fluctuations in PaCO_2 and higher max PaCO_2 were associated with worse neurodevelopmental outcomes in extremely low birth weight infants (McKee et al. 2009). They may indicate either a greater severity of illness or contribution of PaCO_2 to pathophysiology of adverse neurodevelopment. Most importantly, the randomized, controlled trials of permissive hypercapnia in neonates have not reported an increase in intracranial hemorrhage.

27.4 Clinical Data

Due to the beneficial results in adult randomized trials (Petrucci and Iacovelli 2004) and the association between hypocapnia and poor pulmonary and neurodevelopmental outcomes (Collins et al. 2001), permissive hypercapnia has emerged as a potential strategy to decrease morbidity in neonates. Two retrospective studies in neonates reported that higher PaCO_2 values were associated with less lung injury (Kraybill et al. 1989; Garland et al. 1995). Kraybill and colleagues (1989) performed a multicenter analysis on 235 infants whose birth weights were between 751 and 1,000 g before the introduction of surfactant administration. Garland and coworkers (1995) analyzed data on 188 infants weighing less than 1,700 g who received surfactant. Both of these studies concluded that ventilatory strategies leading to early hypocapnia resulted in an increased risk of BPD (odds ratio [OR] of 1.45 and 95 % confidence intervals [CI] of 1.04, 2.01 and OR of 4.3 and 95 % CI of 1.5, 12.0, respectively). Peak levels of PaCO_2 greater than 50 mmHg in the first 4 postnatal days and greater than 40 mmHg before the administration of surfactant were associated with a lower incidence of BPD in these two studies. A population-based study of 407 infants younger than 28 weeks or less than 1,000 g using historic controls also suggested that permissive hypercapnia resulted in a decreased rate of BPD (Kamper et al. 2004). The observations that low

PaCO₂ values during the first days after birth are associated with more lung disease are counter-intuitive at first glance. The usual assumption is that infants who have lower PaCO₂ values have less severe pulmonary disease and are at lower risk of lung injury. However, low PaCO₂ values may reflect ventilator management strategies that result in overventilation in infants who have favorable lung compliance. This mechanism could be an important cause of lung injury, particularly in neonates who have less severe lung disease. Thus, it is possible that ventilatory strategies that target mild hypercapnia or prevent hypocapnia result in reduced incidence or severity of lung injury (Carlo 2007). Retrospective studies in neonates who have congenital diaphragmatic hernia, including the data on 1,210 neonates from 53 centers of the Congenital Diaphragmatic Study Group, reported that permissive hypercapnia resulted in an increase in survival (Bagolan et al. 2004; Dudell and CDH Study Group 2006) and a decreased need for extracorporeal membrane oxygenation (Dudell and CDH Study Group 2006).

There are two situations in which PaCO₂ levels could be allowed to rise a little over “normal” values: first, the neonate with respiratory distress who has not been intubated and in whom neonatologists tolerate higher PaCO₂ levels precisely to avoid intubation and its associated risks (endotrauma, volutrauma, biotrauma) and, second, the neonate who is already on the ventilator in whom higher PaCO₂ levels are accepted to avoid high ventilator settings.

27.4.1 Neonates with Respiratory Distress but Not Intubated

After the report by Avery et al. (1987) on 1987 showing the lowest rate of BPD in the center in which physicians practiced a permissive hypercapnia approach, several investigators have focused on the advantages of an early CPAP strategy. Avery’s publication was a retrospective analysis of 1,625 VLBW infants born between 1982 and 1984 in eight centers. Overall survival was 78–84 %, and BPD rate was significantly lower in Columbia, where 42 % of those infants had received

mechanical ventilation and 37 % had been treated with early CPAP. The “Columbia approach,” as it was started to be called, included early nasal CPAP and acceptance of PaCO₂ levels as high as 60 mmHg. By that time, the same group was proposing a “gentler” approach to manage term neonates with PPHN (Wung et al. 1985), avoiding the widespread hyperventilation-hyperoxemic strategy. Unfortunately, the approach was not scientifically tested until recent years.

In 2000, Van Marter et al. (2000) published a cohort study including 441 VLBW infants (500–1,500 g) trying to identify variables associated with the development of BPD. The study compared outcomes in three clinical centers, and again, Columbia had a much lower rate of BPD, with lower use of surfactant and higher use of early CPAP. A multivariate analysis showed that intubation significantly increased the risk of BPD (OR 13.4, 95 % CI 5.9–30.7 on the day of birth).

In 2005, Ammari et al. (2005) shared the Columbia experience in a publication that intended to find variables associated with early CPAP failure in VLBW infants. They found the following ORs: GA (each week), 0.53 (0.43–0.65); PPV in the delivery room, 2.37 (1.02–5.52); AaPO₂ >180 mmHg, 2.91 (1.30–6.55); and severe RDS by X-ray, 6.42 (2.75–15). It was interesting that 92 % of infants between 1,000 and 1,250 g were successfully managed with early nasal CPAP, while the percentage was 33 % for those infants with BW below 700 g.

It is known that early surfactant administration reduces mortality and respiratory morbidity while the use of mechanical ventilation increases the risk for bronchopulmonary dysplasia. So, over the last few years, one of the controversies in the management of extremely preterm infants has been whether to intubate and give early surfactant or to start early nasal CPAP, avoiding intubation (Finer 2006).

Several observational studies, most with a “before-after” design, suggest that the use of early nasal CPAP reduces BPD rates (Dunn and Reilly 2003; Bohlin et al. 2008). Expert opinions abound on this issue, and even when (following Roman philosopher Seneca) opinions should be weighed and not just counted, they are the “lowest

level of evidence.” Neonatologists have learned that the best way to protect neonates from “good ideas” is to test these ideas in randomized control trials.

27.4.1.1 Randomized Controlled Trials

A few years ago, two studies evaluated the potential beneficial effects of prophylactic nasal CPAP in preterm infants beginning in the delivery room. Sandri et al. (2004) performed an RCT in 17 NICUs in Italy, including 230 neonates 28–31 weeks of whom 80 % had received antenatal steroids. One group was managed with prophylactic nasal CPAP and the other one with “rescue” nCPAP if the infant required $\text{FiO}_2 > 0.4$. Both the use of surfactant (22 %) and mechanical ventilation (12 %) were similar between the two groups. There were no significant differences in other relevant outcomes.

In another multicenter trial, Finer et al. (2004) evaluated the feasibility of implementing prophylactic nasal CPAP in younger infants. This was a pilot study from the NICHD Neonatal Network in which 104 extremely preterm infants (23–27 weeks of GA) were randomized to nCPAP (or use of PPV with PEEP) in the delivery room or to starting nCPAP once in the NICU. Ninety-eight percent of the mothers received antenatal steroids. While the study showed that the very early CPAP approach was feasible, there were no differences between the two groups in any of the major outcomes analyzed. An interesting observation of this study was that 20 % of these ELBW infants were never intubated within the first week of life.

More recently, two RCT addressing this issue have been published. The COIN trial (Morley et al. 2008) (Cpap Or Intubation) included 613 neonates of 25–28 weeks of GA who had spontaneous respiration after birth and signs of respiratory distress. They were randomized to a nasal CPAP group (8 cm H_2O) or to a group with intubation and mechanical ventilation soon after birth (in the delivery room). Patients in the CPAP group received mechanical ventilation if they had recurrent apneas, a $\text{pH} < 7.25$ with $\text{PaCO}_2 > 60$ mmHg, or FiO_2 requirements > 0.6 (to keep $\text{SpO}_2 > 90$ %). The primary outcome was death or BPD (O_2 at 36 weeks). The results were that CPAP failure

(intubation requirement within the first 5 days) was 46 %, and the rate of death or BPD was similar in both groups (CPAP 34 %; MV 39 %, OR 0.8; 95 % CI 0.58–1.12) but with a trend for improved outcomes in the CPAP group. While there were no differences in most of the secondary outcomes, the incidence of pneumothorax was three times higher in the CPAP group. It has been speculated that either the high CPAP level (8 cm H_2O) or the delay in the use of surfactant might be responsible for this difference. In subgroup analyses, the rate of death or BPD was almost the same for the most immature infants (25–26 weeks) with a trend to lower incidence within infants 27–28 weeks in the CPAP group (24.6 % versus 31.3 %; OR 0.72; 95 % CI 0.46–1.11).

The NICHD Neonatal Network designed the SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial) trial to compare early CPAP treatment with early surfactant treatment in extremely preterm infants (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al. 2010). This was a multicenter trial with a factorial design, in which there was another intervention that was being tested (different SpO_2 target levels). It should be noted that in this study, not only an early CPAP strategy was tested but also a whole ventilator management, as the authors compared a strategy of treatment with CPAP and protocol-driven limited ventilation begun in the delivery room and continued in the neonatal intensive care unit (NICU) with a strategy of early intratracheal administration of surfactant (within 1 h after birth) followed by a conventional ventilation strategy. Extubation criteria, for example, were different for the two groups. In terms of PaCO_2 levels, the threshold for the CPAP group was 65 mmHg (both for intubation and for extubation), while it was 50 mmHg for extubation in the control group (showing that even in the standard group, higher-than-“normal” PaCO_2 levels are currently being accepted). The primary outcome was death or BPD (O_2 at 36 weeks). The study included 1,316 preterm infants 24–27 weeks of GA. The rates of the primary outcome did not differ significantly between groups (48.7 % versus 54.1 %) but again favored the CPAP group.

The adjusted relative risk for CPAP was 0.91; 95 % CI 0.83–1.01.

The Neocosur South American Network has recently presented the results of another multicenter RCT (Tapia et al. 2012). This study was designed to determine if a strategy of prophylactic bubble CPAP in VLBW infants could decrease the need for mechanical ventilation during the first week of life without affecting major morbidity/mortality. Two hundred and fifty-six infants (800–1,500 g) were randomized to either bubble CPAP (5 cm H₂O) or oxyhood if they were breathing spontaneously at 5 min of age. Intubation was performed if FiO₂ >0.35, but in the CPAP group, infants were extubated within 10 min after surfactant administration. Infants were kept on CPAP while PaCO₂ was below 60 mmHg and pH >7.20. Mechanical ventilation was received in 30 % of infants in the CPAP group and 52 % in the control group (*p* 0.001). The combined outcome of death or BPD (O₂ at 36 weeks) was 15 % in the CPAP group and 19 % in the control group (RR 0.8, 95 % CI 0.46–1.36). No differences in other outcomes (including gas leaks) were seen between groups.

All these studies compare early CPAP with early surfactant. An interesting “in between” strategy has been proposed originally by investigators in Sweden, combining the beneficial effects of the two treatments (early CPAP and early surfactant) (Verder et al. 1994, 1999, 2009). The “Scandinavian approach” or INSURE method (Intubation, Surfactant, Extubation) consists in intubating the infant for surfactant administration with rapid – within 10 min – extubation to nasal CPAP. Several studies have looked at this strategy, and the results consistently show a reduction in the need for mechanical ventilation. They have been reviewed by the Cochrane Library (Stevens et al. 2007), and the meta-analysis shows a decreased need for mechanical ventilation (RR 0.67; 0.57–0.79), a decrease in BPD at 28 days (RR 0.51; 0.26–0.99), and a decrease in air leak syndromes (RR 0.52; 0.28–0.96).

This systematic revision and meta-analysis has not included the following three recent studies. Rojas et al. (2009) performed a RCT in eight centers in Colombia, including 278 preterm infants (27–31 weeks of GA) with RDS. They were ran-

domized to an INSURE group (with rapid extubation to nasal CPAP) or to a control group, receiving nasal bubble CPAP (6 cm H₂O). The primary outcome was the requirement of mechanical ventilation (following specifically defined criteria: FiO₂ >0.75 for 30 min, persistent or recurrent SpO₂ <80 %, PaCO₂ >65 mmHg + pH <7.22, or clinical deterioration). The use of MV was significantly reduced (39–26 %, RR 0.69; 0.49–0.97) and the rate of gas leaks was also reduced from 9 % in the control group to 2 % in the treatment group (RR 0.25; 0.07–0.85). The combined outcome of death or BPD (O₂ at 36 weeks) was 54 % in the CPAP group and 63 % in the control group (RR 0.86, 95 % CI 0.7–1.04). There were no differences in mortality or any secondary outcome measure.

Sandri et al. (2010) recently published the CURPAP study, an international randomized controlled trial, designed to evaluate the efficacy of combining prophylactic surfactant and early nasal CPAP in preterm infants. The purpose of this study was to compare the administration of prophylactic surfactant followed by nCPAP versus early nCPAP institution with early rescue surfactant. Two hundred and eight newly born infants (25–28 weeks) with respiratory insufficiency but spontaneous respirations were randomized to a group of prophylactic surfactant and rapid extubation to nCPAP or to an nCPAP group (6–7 cm H₂O) with rescue surfactant if needed. The CPAP failure definition was the same for both groups and considered any of the following: FiO₂ requirement >0.4 to maintain SpO₂ 85–92 % for at least 30 min, significant apnea, respiratory acidosis defined as PaCO₂ >65 mmHg and pH <7.20, or clinical deterioration. The primary outcome measure was the need for mechanical ventilation within the first 5 days of life. No differences were found in either the primary (31 % versus 33 %) or secondary outcome measures, except in the use of surfactant. The combined outcome of death or BPD (O₂ at 36 weeks) was 21 % in the CPAP group and 22 % in the control group. There was a trend over a higher rate of pneumothorax in the INSURE group (6.7 % versus 1 %). In this study, prophylactic surfactant was not superior to early rescue surfactant in decreasing the need for MV and the incidence of main morbidities of prematurity in spontaneously breathing 25–28 weeks preterm infants on nCPAP.

Table 27.2 BPD/death in major trials of early CPAP

Trial	CPAP (%)	Control (%)	ARR (%)
COIN (Morley et al. 2008) (<i>n</i> = 613)	34	39	5
SUPPORT (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al. 2010) (<i>n</i> = 1,316)	49	54	5
VON (Dunn et al. 2011) (<i>n</i> = 648)	30	36	6
Neocosur (Tapia et al. 2012) (<i>n</i> = 256)	15	19	4
Colombia (Rojas et al. 2009) (<i>n</i> = 278)	54	63	9
CURPAP (Sandri et al. 2010) (<i>n</i> = 208)	21	22	1

Crude analysis shows that the rate of death or BPD was CPAP, 613/1,568 (39 %) versus Vent, 680/1,532 (44 %). ARR: 5. NNT: 20. RR 0.88 (95 % CI 0.81–0.96)

Finally, the Vermont Oxford Neonatal Network has recently presented the results of a trial on delivery room management of preterm infants at risk for RDS (Dunn et al. 2011). The objective was to determine whether prophylactic surfactant followed by a period of assisted ventilation (ProphS) compared with either intubation-surfactant treatment and rapid extubation to nasal CPAP (INSURE) or early stabilization on nasal CPAP (nCPAP) is superior in preventing BPD or death in infants at risk of RDS. Six hundred and forty eight infants (26–29 weeks) were enrolled at 27 centers and randomly assigned to these three groups prior to delivery. In the nCPAP group, surfactant was administered if intubation was required, by the following criteria: severe apnea, $\text{PaCO}_2 > 65$ mmHg, $\text{FiO}_2 > 0.6$, and severe respiratory distress. The trial was terminated prior to reaching the desired sample size (876) due to difficulties with enrollment. Ninety-eight percent of the mothers received antenatal steroids. Fewer infants in the nCPAP versus the ProphS group received surfactant (46 versus 99 %) and were ventilated (45 versus 96 %) during the first week of life. While no significant differences were seen in the primary outcome of death or BPD at 36 weeks postmenstrual age, the trends favored the nCPAP group (30.5 % versus 36.5 % in the ProphS group; RR 0.83, 95 % CI 0.64–1.09). There were no statistically significant differences in mortality, other complications of prematurity or the composite outcome of death, or major morbidity (severe ROP, BPD, and PVL or severe IVH).

These trials show that early nasal CPAP is slightly superior to the standard practice of early surfactant. Early NCPAP can avoid intubation and treatment with surfactant thereby resulting in comparable or improved outcomes and poten-

tially at reduced costs. More importantly, the combined outcome of death or BPD is consistently lower among trials, and crude analysis suggests a beneficial effect (Table 27.2). Three recent meta-analyses have reported reduced BPD or death, favoring a strategy of early nasal CPAP over prophylactic surfactant or intubation and MV. Rojas-Reyes et al. (2012), in a Cochrane meta-analysis including two trials that evaluated prophylactic surfactant found an increase in BPD or death in comparison to a strategy of early nasal CPAP and selective intubation [OR 1.12 (95 % CI 1.02–1.24)] Schmölzer et al. (2013) performed a meta-analysis of four trials that evaluated the effect of early nasal CPAP compared with intubation and mechanical ventilation. Similar to Rojas-Reyes et al., they reported a beneficial effect of early nasal CPAP [OR 0.91 (95 % CI 0.84–0.99)]. Finally, Fischer and Bühner (2013) have done a meta-analysis of trials assessing the effect of strategies to avoid endotracheal mechanical ventilation on the incidence of BPD or death. Seven trials were included (two of them evaluating surfactant application during nCPAP via a thin catheter) and the findings also favor a strategy of early nasal CPAP [OR 0.83 (95 % CI 0.71–0.96)]. It is important, however, to keep in mind the potential beneficial effects of early surfactant in patients treated with early CPAP. As stated in a recent European consensus (Sweet et al. 2013), while a policy of early CPAP should be standard, based on the clinical trials that showed benefits of early CPAP, infants should be given surfactant early in the course of RDS if the FiO_2 goes above 0.3 to 0.5. Judicious use of mechanical ventilation and prompt weaning off ventilation may also be beneficial. In addition, none of these studies

have detected adverse outcomes, so allowing PaCO₂ levels to be below 60–65 mmHg in this population during the first days after birth appears to be safe.

27.4.2 Neonates with Respiratory Distress on Mechanical Ventilation

The use of permissive hypercapnia has been recognized as a strategy that helps to reduce the risk of BPD in preterm neonates requiring assisted ventilation and was included in the “potentially better practices” by the Breathsavers Group of the Vermont Oxford Network Neonatal Intensive Care Quality Improvement Collaborative (Payne et al. 2006a, b).

It is important that a consensus is reached in terms of what permissive hypercapnia is (and what it is not). The most accepted definition of permissive hypercapnia is that it is a ventilator strategy in which low tidal volumes are used, accepting PaCO₂ levels above “normal” to decrease the risks of volutrauma. The potential advantages of low tidal volume ventilation in preterm neonates appear to be related both to less injurious alveolar opening and closing cycles and to the avoidance of hypocapnia – with all its known adverse effects. While it was initially thought that the potential benefits of high PaCO₂ (a consequence of the ventilatory strategy) were related to “gentler” ventilation, it is now known from the animal and adult literature that hypercapnia per se may have some beneficial effects. As it was mentioned earlier, “therapeutic hypercapnia” a term that refers to the deliberate induction of hypercapnia by increasing inspired CO₂ places the emphasis on CO₂ as a therapeutic agent rather than as a necessary by-product of ventilation strategies applied with the goal of limiting lung injury. This has already been covered in a previous section of this chapter.

This ventilatory strategy can be also called low tidal volume ventilation, but the name was started to be used when it was uncommon to measure tidal volume in routine mechanical ventilation in neonates, and the term “permissive hypercapnia”

was then widespread and accepted. In addition, as have been seen earlier, high PaCO₂ levels may have beneficial effects independently of the way by which they are achieved. An important point is the definition of the safe range of PaCO₂ levels in neonates during the first days of life. Based on published data, it appears that keeping PaCO₂ between 40 and 60 mmHg with a pH >7.2 should not increase the risk of neurologic damage.

However, there is still a misunderstanding, and some erroneously consider “permissive hypercapnia” as a synonymous of plain hypercapnia. PaCO₂ can be high for different situations, such as inadequate ventilation, ETT obstruction, gas leak syndromes, and PDA. It may be obvious, but hypercapnia as a result of clinical problems that are overlooked is not “permissive hypercapnia” and we should probably call it “negligent hypercapnia.” Another error is tolerating very high PaCO₂ levels reaching values that imply potential risks for the neonate. Again, this should not be called “permissive hypercapnia” but probably “iatrogenic hypercapnia.” It is difficult to define a limit above which the PaCO₂ levels are dangerous for the preterm neonate during the first few days of life. The articles by Fabres et al. and McKee et al. about the risks of IVH and neurodevelopmental impairment associated with both extremes of PaCO₂ during the first days in preemies are interesting and concerning (Fabres et al. 2007; McKee et al. 2009).

As we know, avoidance of mechanical ventilation is the best way to reduce ventilator-induced lung injury. Should the infant need ventilation, use of surfactant, low tidal volume ventilation, adequate PEEP levels, FiO₂ to target SpO₂ around 91–95 % based on the SUPPORT trial, and keeping PaCO₂ between 45 and 55 mmHg or slightly higher during the first days after birth appears to be a reasonable strategy (and extubation ASAP!). To decrease the risk of PaCO₂ fluctuations and undesired values, the use of transcutaneous CO₂ monitors in these preemies should be considered. After the first days of life, higher PaCO₂ levels could be tolerated as the infant develops compensated respiratory acidosis.

Thus, permissive hypercapnia is a ventilatory strategy by which relatively high PaCO₂ levels are accepted to avoid high tidal volumes, lung

overdistension, and hypocapnia, potentially reducing ventilator-induced lung injury. To maintain “normocapnia” in some patients with severe respiratory distress requires high ventilator settings, increasing the risk of ventilator-induced lung injury. It is known that compensated respiratory acidosis is well tolerated. Strategies that lead to hypocapnia can increase the incidence of BPD, as have been shown by several authors (Kraybill et al. 1989; Garland et al. 1995).

27.4.2.1 Randomized Controlled Trials

Three randomized, controlled trials of permissive hypercapnia have been performed in intubated neonates. The first pilot trial randomized 49 preterm infants who had respiratory distress syndrome to a target PaCO_2 of 35–45 mmHg or 45–55 mmHg for the first 4 postnatal days (Mariani et al. 1999). The need for assisted ventilation was decreased in the permissive hypercapnia group during the intervention period. There also was a trend toward a decrease in the total number of days on assisted ventilation in the permissive hypercapnia group at 2.5 (1.5–11.5) days compared with 9.5 (2.0–22.5) days in the normocapnia group (p 0.17). The National Institutes of Health multicenter trial randomized 220 infants of 501–1,000 g birth weight to a PaCO_2 target below 48 mmHg or above 52 mmHg during the first 10 postnatal days (Carlo et al. 2002). Although the study was underpowered because of early termination, there was a trend toward a lower incidence of BPD or death in the hypercapnia group (63 % versus 68 %). Significantly fewer infants required ventilator support at 36 weeks postmenstrual age in the permissive hypercapnia group compared with infants in the routine ventilation group (1 % versus 16 % $P < 0.01$). The incidence of severe intraventricular hemorrhage and periventricular leukomalacia was comparable between the groups. Survival without neurodevelopmental impairment at 18–22 months corrected age occurred in 36 % of infants randomized to permissive hypercapnia and 32 % of those randomized to the control group. The differences in neurodevelopmental impairment (51 % versus 55 %) and cerebral palsy (11 % versus 20 %) were not statistically significant but favored the minimal ventilation group. A third small trial

($n=65$) of higher PaCO_2 targets (55–65 mmHg) in more immature infants did not reveal benefits of permissive hypercapnia (Thome et al. 2006). The 2001 meta-analysis of permissive hypercapnia included the only three outcomes common to the two included trials. The incidences of death or BPD at 36 weeks postmenstrual age, intraventricular hemorrhage grade 3 or 4, or periventricular leukomalacia were not statistically different. The meta-analysis concluded that due to insufficient evidence, permissive hypercapnia could not be recommended uniformly to reduce overall mortality or pulmonary/neurodevelopmental morbidity in preterm infants (Woodgate and Davies 2001).

Conclusions

Avoidance of mechanical ventilation with the early use of nasal CPAP is safe and appears to be beneficial. The combined outcome of death or BPD is consistently lower among trials even though the effect size was smaller than hypothesized. Although none of them have shown statistically significant differences, three recent meta-analyses show a significant decrease in the combined outcome of death or BPD, with NNTs between 17 and 35. On ventilated patients, permissive hypercapnia is a ventilatory strategy that may reduce injury to the developing lung through a variety of mechanisms. Based on the current literature, pertinent physiologic rationale and experimental research suggest that permissive hypercapnia may be beneficial. Avoidance of extreme levels of PaCO_2 and fluctuations may be important to decrease risks of neurologic damage. While it is difficult to define the safe limits of PaCO_2 for the preterm neonate, based on some studies it seems that PaCO_2 should be kept above 45 mmHg as long as the pH is above 7.20, during the first few days of life. Higher PaCO_2 could be accepted afterward when there are fewer concerns about cerebral blood flow regulation and there is a partially compensated respiratory acidosis. Continued basic science and clinical research must be conducted to clarify the appropriate clinical application, optimal level of hypercapnic acidosis, and safety of hypercapnic acidosis in preterm infants.

Essentials to Remember

- Avoidance of mechanical ventilation with the early use of nasal CPAP with permissive hypercapnia is safe and beneficial, decreasing the rate of death or BPD.
- Physiologic rationale and experimental research suggest that permissive hypercapnia as a ventilatory strategy in preterm neonates may be beneficial.
- Permissive hypercapnia in neonates exerts its beneficial effects through a variety of mechanisms, including low tidal volume ventilation, hypercapnic acidosis per se, and avoidance of hypocapnia.
- Permissive hypercapnia appears to be safe in neonates, but concern exists about risks of loss of cerebral blood flow autoregulation in preemies. Fluctuations in PaCO₂ should be avoided.

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Part X

Adjunctive Therapies in Mechanically Ventilated Children and Neonates

28.1 Pulmonary Surfactant and Exogenous Surfactant Therapy in Neonates

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Educational Aims

- Understand the composition, metabolism, and physiology of pulmonary surfactant
- Understand the effect of surfactant in infants with surfactant deficiency or dysfunction
- Understand the optimal timing and methods of surfactant administration

28.1.1 Introduction

Exogenous pulmonary surfactant, widely used in neonatal care, is one of the best-studied treatments in neonatology, and its introduction in the 1990s led to a significant improvement in neonatal outcomes in preterm infants, including a decrease in mortality. This chapter provides an overview of surfactant composition and function in health and disease and summarizes the evidence for its clinical use.

28.1.2 Surfactant Composition, Metabolism, Physiology, and Pathophysiology

28.1.2.1 Surfactant Composition and Metabolism

The alveoli of all mature mammals are lined with pulmonary surfactant, a lipoprotein that reduces surface tension and prevents alveolar collapse. The constituents of surfactant are phospholipids (80 %), neutral lipids (8 %), and proteins (20 %). Among the phospholipids, the predominant one (60 %) is dipalmitoylphosphatidylcholine (DPPC), with lesser amounts of unsaturated phosphatidylcholine compounds, phosphatidylglycerol, and phosphatidylinositol. The proteins consist of four unique surfactant-associated apoproteins. Two of these, SP-A and SP-D, are hydrophilic proteins and belong to a subgroup of mammalian lectins called collectins. The other two, SP-B and SP-C, are hydrophobic proteins.

Surfactant is produced in the type II cells of the alveoli (Fig. 28.1), which differentiate between 24 and 34 weeks of gestation in the human. It is assembled and stored in the lamellar bodies, which are concentric or parallel lamellae of phospholipid bilayers. Lamellar bodies are extruded into the fluid layer lining the alveoli by exocytosis and form long stacked tubes composed mainly of

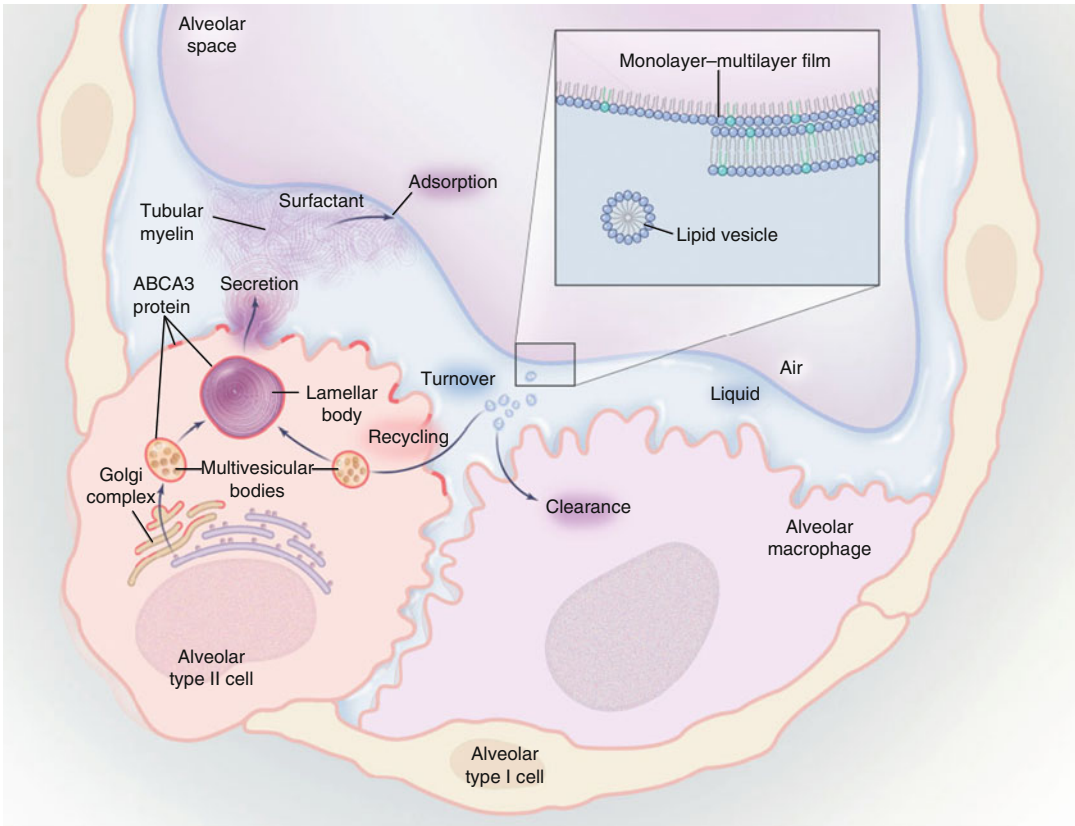


Fig. 28.1 Lung surfactant and the lamellar body. The composition of lung surfactant is critical to lung function, and the subcellular lamellar body of the type II alveolar cell has a major role in maintaining the composition of surfactant. The distribution of ATP-binding cassette (ABC) transporter A3 (*ABCA3*) is shown in red. It is possible that *ABCA3* targets surfactant-containing vesicles to the lamellar bodies. The lamellar body is formed through the fusion of several multivesicular bodies, and its lipid bilayers are converted to tubular myelin as they are turned out into the alveolar space. Surfactant protein A, secreted primarily by a constitutive pathway that does not involve the lamellar body, is required for the formation of tubular

myelin. Surfactant aggregate, such as tubular myelin, is the precursor of surfactant at the air–water interface (*inset*). Cationic transmembrane proteins (surfactant protein B or surfactant protein C or both (not depicted in the monolayer–multilayer film)) together with anionic phospholipids (phosphatidylglycerol or phosphatidylinositol or both (*green*)) facilitate the entry of dipalmitoylphosphatidylcholines (*blue*) into the monolayer at the interface, maintaining a low surface tension. During tidal breathing, tubular myelin surfactant is converted to smaller aggregates that are taken up by type II cells and alveolar macrophages. Arrows depict the direction of surfactant flux

phospholipid bilayers called tubular myelin. On cross section, tubular myelin has a lattice-like structure because the corners of the component tubes appear fused. Tubular myelin enters the air–water interface quickly by adsorption and greatly reduces the surface tension of that interface (Hallman 2004). It is the major source of the monolayer surface film lining the air–liquid

interface in the alveoli. In this monolayer the hydrophobic fatty acyl groups of the phospholipids extend into the air, while the hydrophilic polar head groups bind water (Possmayer et al. 1984).

The total pulmonary surfactant content can be divided into an intra-alveolar and an intracellular pool (Nkadi et al. 2009). However, the total surfactant pool size is not equivalent to the amount

of active surfactant. Maintaining an adequate intra-alveolar surfactant pool is essential for lung function and is dependent on the dynamic cycle of surfactant metabolism (Nkadi et al. 2009). Surfactant pool size increases in late pregnancy, followed by a gradual decrease after birth to adult values (Zimmermann et al. 2005). During and shortly after birth, large amounts of surfactant are released into the alveolar space (Zimmermann et al. 2005). Among different species, humans have the smallest alveolar pool sizes, whereas the amount of saturated phosphatidyl choline in lung tissue is similar across species. The lower alveolar surfactant pool size makes the human lung particularly vulnerable to surfactant dysfunction in case of lung injury. The surfactant pool size in preterm infants with respiratory distress syndrome (RDS) is around 10 mg/kg or less, while healthy term infants have an estimated surfactant pool size of 100 mg/kg (Nkadi et al. 2009). The rate of synthesis of surfactant in preterm infants is also low (Zimmermann et al. 2005).

Alveolar surfactant can be cleared by different pathways. All the main components of surfactant (DPPC, PG, SP-A, SP-B, and SP-C) are recycled. The phospholipid from the monolayer eventually reenters the type II cells through endocytosis and forms multivesicular bodies, which are then either incorporated into lamellar bodies (“recycled”) or degraded in lysosomes. Degraded surfactant components are also used to synthesize new surfactant lipids or proteins. Finally, surfactant can be removed from the lung, either as intact molecules or as degraded products (Zimmermann et al. 2005; Jobe and Ikegami 1993).

Control of surfactant secretion: Surfactant secretion can be stimulated by a number of mechanisms. Type II cells have beta-adrenergic receptors and respond to beta-agonists with increased surfactant secretion (Nkadi et al. 2009). Purines, such as adenosine triphosphate are potent stimulators of surfactant secretion and may be important for its secretion at birth. Mechanical stretch, such as lung distension and hyperventilation, has also been found to be involved in stimulating surfactant secretion

(Nkadi et al. 2009). Hormones also play a role in surfactant secretion. Thyroxine accelerates type II cell differentiation while acting synergistically with glucocorticoids to enhance lung compliance and DPPC synthesis. Finally, both prenatally administered maternal glucocorticoids and exogenous surfactant administration after birth stimulate endogenous surfactant synthesis.

28.1.2.2 Surfactant Physiology

28.1.2.2.1 In the Normal Lung

Pulmonary alveoli are bubble shaped, with a high degree of curvature. The attraction between the molecules in the alveolar fluid of the moist inner surface of the alveoli generates surface tension and tends to make the alveoli collapse. Unchecked, this tendency would result in lung collapse. Surfactant greatly reduces the surface tension at the air–liquid interface in the alveoli and distal bronchioles. This prevents the alveoli from collapsing during expiration and promotes lung expansion during inspiration.

The main component responsible for decreasing the surface tension is DPPC. However it adsorbs very slowly to air–liquid interfaces and therefore requires surfactant proteins or other lipids to facilitate its adsorption. SP-B and SP-C enhance spreading of phospholipid in the air-spaces. SP-B promotes phospholipid adsorption and induces the insertion of phospholipids into the monolayer, thus enhancing the formation of a stable surface film (Creuwels et al. 1997). SP-C enhances phospholipid adsorption, stimulates the insertion of phospholipids out of the subphase into the air–liquid interface, and may increase the resistance of surfactant to inhibition by serum proteins or by edema fluid (Creuwels et al. 1997; Griesse 1999).

As the alveolar surface expands during inspiration, surfactant components insert from the hypophase (epithelial lining fluid) into the monolayer. At expiration the alveolar surface reduces and the monolayer is compressed, thereby squeezing out some surfactant proteins, unsaturated PC, and other lipids. By this mechanism, the monolayer comprises mainly of

DPPC, the most important surface-tension-lowering component during compression (Zimmermann et al. 2005).

Surfactant also has a role in pulmonary host defense. SP-A and SP-D may play important roles in the defense against inhaled pathogens, and SP-A may have a regulatory function in the formation of the monolayer that lowers the surface tension (Creuwels et al. 1997).

28.1.2.2.2 In the Premature Lung

The preterm infant with respiratory distress syndrome (RDS) has immaturity of the lungs, especially of the type II cells, and decreased synthesis of surfactant. This results in low amounts of surfactant in the alveoli (surfactant pool size of 2–10 mg/kg) (Zimmermann et al. 2005) that contains a lower percent of disaturated phosphatidylcholine species, less phosphatidylglycerol, and less of all the surfactant proteins than surfactant from a mature lung. Minimal surface tensions are also higher for surfactant from preterm than term infants (Nkadi et al. 2009). However, preterm infants may have increased recycling of surfactant when compared to term infants (Zimmermann et al. 2005).

Shortly after birth, infants with RDS develop tachypnea, grunting, nasal flaring, use of accessory muscles of respiration, intercostal or subcostal retractions, cyanosis, poor feeding, and apnea. A chest radiograph typically shows a diffuse reticulogranular “ground glass” opacification (the result of diffuse alveolar atelectasis) with superimposed air bronchograms (Nkadi et al. 2009). The lungs of infants who die from RDS show alveolar atelectasis, alveolar and interstitial edema, and diffuse hyaline membranes in distorted small airways (Nkadi et al. 2009). RDS is one of the most common causes of death and morbidity in preterm neonates. It occurs worldwide with a slight male predominance (Nkadi et al. 2009). Prenatal corticosteroids significantly reduce the incidence, severity, and mortality associated with RDS.

28.1.2.2.3 In the Injured Neonatal Lung

Surfactant dysfunction can develop secondary to a variety of other conditions that result in

lung injury in neonates, such as meconium aspiration syndrome, pulmonary hemorrhage, and pneumonia.

In meconium aspiration syndrome, the mechanisms underlying surfactant inactivation are not fully understood, but it has been shown that meconium destroys the fibrillary structure of surfactant and decreases its surface adsorption rate (Nkadi et al. 2009). In vitro studies (Moses et al. 1991; Clark et al. 1987) and animal studies (Sun et al. 1993; Davey et al. 1993) have demonstrated that meconium inhibits surfactant function and is likely to be partially responsible for alveolar collapse in meconium aspiration syndrome. Components of meconium that may contribute to altered surfactant function include cholesterol, free fatty acids, bile salts, bilirubin, and proteolytic enzymes (Moses et al. 1991; Clark et al. 1987; Sun et al. 1993; Lieberman 1966). In particular, phospholipase-A2 (PLA2) in meconium has been found to inhibit the activity of surfactant in vitro in a dose-dependent manner, through the competitive displacement of surfactant from the alveolar film (Nkadi et al. 2009). PLA2 is also known to induce hydrolysis of DPPC, releasing free fatty acids and lyso-PC which damage the alveolar–capillary membrane and induce intrapulmonary sequestration of neutrophils (Nkadi et al. 2009).

In pulmonary hemorrhage, capillary filtrate builds up in the interstitial space and can burst through the pulmonary epithelium into the airspaces. Neutrophils are released following endothelial damage and they, in turn, express proteases, oxygen free-radicals, and cytokines. These free oxygen molecules damage the type II cells that produce surfactant proteins, thus inhibiting production of the proteins (Nkadi et al. 2009). Elastase, one of these proteases, damages and degrades SP-A, thereby inhibiting SP-A-mediated surfactant lipid aggregation and adsorption in vitro (Nkadi et al. 2009).

Acute respiratory distress syndrome (ARDS) is a significant cause of morbidity and mortality in all age groups following infection (the most common cause), hemorrhage, or other forms of lung injury. It is defined as a severe form of acute lung injury (ALI) and a syndrome of acute

pulmonary inflammation. ALI/ARDS is characterized by sudden onset, impaired gas exchange, decreased static compliance, and a non-hydrostatic pulmonary edema (Nkadi et al. 2009). ARDS is characterized by an increase in the permeability of the alveolar–capillary barrier due to injury to the endothelium and/or alveolar lining cells. Damage to the alveolar type I cells leads to an influx of protein-rich edema fluid into the alveoli, as well as decreased fluid clearance from the alveolar space. Neutrophils are attracted into the airways by host bacterial and chemotactic factors and express enzymes and cytokines which further damage the alveolar epithelial cells (Nkadi et al. 2009). Type II epithelial cell injury leads to a decrease in surfactant production, with resultant alveolar collapse.

28.1.2.2.4 Effect of Mechanical Ventilation on Pulmonary Surfactant

Mechanical ventilation in itself can worsen lung disease and effect surfactant function. The damage caused by mechanical ventilation can cause fluid, protein, and blood to leak into the airways, alveoli, and the lung interstitium, interfering with lung mechanics, inhibiting surfactant function, and promoting lung inflammation (Clark et al. 2001). Even a short period of mechanical ventilation can cause a decrease in lung compliance that is associated with a large influx of proteins into the alveolar space and with alterations in the pulmonary surfactant system (Veldhuizen et al. 2000). The changes of surfactant in these experiments are different from those seen in acute lung injury, indicating that they may represent an initial response to mechanical ventilation.

In the adult lung, injuries due to mechanical ventilation occur primarily when the sum of the functional residual capacity (FRC) and tidal volume approach or exceed maximal lung volume (Dreyfuss and Saumon 1993). The preterm lung is particularly susceptible to injury by mechanical ventilation because of structural immaturity, and tidal volumes considered safe for the adult may approach the maximum lung volumes in the preterm lung (Wada et al. 1997). Initiation of ventilation in preterm lambs with high volumes causes lung injury and decreases the subsequent

response to surfactant treatment (Wada et al. 1997).

In premature baboons, mechanical ventilation results in abnormal surfactant metabolism (Seidner et al. 1998). In the normal lung, large lipid arrays or large-aggregate forms of surfactant are the source of the surface film (Wright 1990). Small vesicles, primarily containing lipids, reenter the hypophase for recycling or catabolism. The amount of inactive vesicular forms increases with lung injury, and this increase is associated with a deterioration in lung mechanics.

Long-term ventilation of the lungs in immature preterm infants with respiratory distress leads to ventilator-induced lung injury and chronic lung disease. Ventilation of these infants not only interferes with alveolarization but also with the surfactant system. Ventilated preterm animals accumulated very large lipid pools in tissue, but alveolar pools stay relatively low indicating decreased secretion of newly synthesized saturated phosphatidylcholine and increased catabolism. These effects of both acute and long-term ventilation leave the preterm infant particularly susceptible to problems associated with surfactant deficiency and dysfunction.

28.1.3 Exogenous Surfactant Therapy

28.1.3.1 Types of Exogenous Surfactant

There are two broad categories of exogenous surfactant available for treatment: animal-derived surfactants and synthetic surfactants.

28.1.3.1.1 Animal-Derived Surfactants

These include the following:

Bovine surfactant obtained by lung mince:

Beractant (Survanta) and Surfactant-TA (Surfacten) are lipid extracts of bovine lung mince with added DPPC, tripalmitoylglycerol, and palmitic acid.

Bovine surfactant obtained by lung lavage: Calf lung surfactant extract (CLSE, calfactant, Infasurf), SF-RI1 (Alveofact), and bovine

lipid extract surfactant (BLES) are bovine lung washes subjected to chloroform–methanol extraction.

Porcine surfactant obtained by lung mince:

Poractant (Curosurf) is a porcine lung mince that has been subjected to chloroform–methanol extraction and further purified by liquid–gel chromatography. It consists of approximately 99 % polar lipids (mainly phospholipids) and 1 % hydrophobic, low molecular weight proteins (SP-B and SP-C) (Wiseman and Bryson 1994).

28.1.3.1.2 Synthetic Surfactants

These include the following:

Protein-free synthetic surfactants: There is one product in this category, colfosceril palmitate, cetyl alcohol, tyloxapol (Exosurf), and it consists of 85 % dipalmitoylphosphatidylcholine (DPPC), 9 % hexadecanol, and 6 % tyloxapol (a spreading agent). Another product in this category, pumactant (also known as artificial lung expanding compound, ALEC) is no longer manufactured (Halliday 2006) and was a 7:3 mixture of DPPC and phosphatidyl glycerol. These synthetic surfactants lack many of the components of animal-derived surfactant, particularly the hydrophobic surfactant proteins B and C.

Protein-containing synthetic surfactants: These surfactants contain synthetic phospholipids along with proteins (produced through peptide synthesis and recombinant technology) that attempt to mimic the function of either SP-B or SP-C. Of these, lucinactant (Surfaxin) contains dipalmitoylphosphatidylcholine, palmitoyl oleoylphosphatidyl glycerol, and palmitic acid (Cochrane et al. 1996, 1998) combined with a mimic of SP-B called sinapultide or KL4 peptide. KL4 is a 21-residue peptide comprised of repeated units of four hydrophobic leucine (L) residues, bounded by basic polar lysine (K) residues arranged in the following order: KLLLLKLLLLKLLLLKLLLLK. This structure resembles the repeating pattern of hydrophobic and hydrophilic residues in the C-terminal part of SP-B and stabilizes the phospholipid layer by interactions with the lipid heads and the acyl chains (Cochrane and Revak 1991). Another

synthetic SP-B analog currently under testing is called dSP-B₁₋₂₅, which resembles the N-terminal segment of SP-B and when combined with synthetic phospholipids has shown some efficacy in animal studies.

Another type of synthetic protein-containing surfactant is called rSP-C surfactant or lusuplutide (Venticute). It contains DPPC, palmitoyl oleoylphosphatidyl glycerol, palmitic acid, and calcium chloride (Hafner and Germann 2000; Spragg et al. 2000) combined with a recombinant SP-C analog (rSP-C), which is similar to the 34-amino acid human SP-C sequence, except that it contains cysteine (in place of phenylalanine) in positions 4 and 5 and contains isoleucine (instead of methionine) in position 32.

During surfactant replacement therapy, exogenous surfactants are given at doses between 10 and 20 times the usual pool sizes found in pre-term infants with RDS, which approximates the pool size in term infants (Nkadi et al. 2009). The table summarizes the individual characteristics of each of these products, including the dosage, volume, and the recommended repeat dosing interval. All these products are administered intratracheally with each dose divided into multiple aliquots and should be administered according to the manufacturers' recommendations (Table 28.1).

28.1.3.2 Administration of Exogenous Surfactant: Practical Issues

The dynamics of how exogenously administered surfactant might spread through the airways into the alveoli have been well studied in the laboratory and theoretical models created (Halpern et al. 1998, 2008). When a bolus of surfactant is instilled and propagates down the airways, it deposits a liquid layer that coats the airways. The bolus may rupture because it may not pick up as much fluid as it is depositing and therefore may not reach the terminal bronchioles and alveoli where it is needed. However, the deposited liquid layer that is left behind may still advance due to the effects of gravity and surface tension, especially as the liquid layer thins.

The potential magnitude of uneven distribution of exogenously administered surfactant has

Table 28.1 Products available for exogenous surfactant therapy

Name of product (pharmaceutical name)	Source	Phospholipid (mg/ml)	Dose (volume) (ml/kg)	Dose (mg/kg of phospholipid)	Repeat dosing interval (h)
<i>Animal-derived products</i>					
Beractant (Survanta)	Lipid extract of bovine lung mince with added DPPC, tripalmitoylglycerol and palmitic acid	25	4	100	6
Calfactant (Infasurf)	Bovine lung wash subjected to chloroform–methanol extraction	35	3	100	6–12
SF-R11 (bovactant, Alveofact)	Bovine lung wash subjected to chloroform–methanol extraction	50	1–2	50–100	8
bLES (BLES)	Bovine lung wash subjected to chloroform–methanol extraction	27	5	135	6
Poractant (Curosurf)	Porcine lung mince that has been subjected to chloroform–methanol extraction and further purified by liquid–gel chromatography	80	1.25–2.5 for initial dose, 1.25 for subsequent doses	100–200	12
<i>Protein-free synthetic surfactants</i>					
Colfosceril palmitate, hexadecanol, tyloxapol	85 % dipalmitoylphosphatidylcholine (85 %), hexadecanol (9 %), and tyloxapol (a spreading agent, 6 %)	13.5	5	67.5	12
<i>Protein-containing synthetic surfactants</i>					
Lucinactant (Surfaxin) (Moya et al. 2005)	Synthetic phospholipids and proteins produced through peptide synthesis and recombinant technology. Contains a mimic of SP-B called sinapultide or KL4 peptide	30	5.8	175	6
Recombinant SP-C surfactant (Venticute) ^a	Synthetic phospholipids and proteins produced through peptide synthesis and recombinant technology. Contains recombinant SP-C (rSP-C) combined with DPPC, palmitoyl oleoylphosphatidyl glycerol, palmitic acid, and calcium chloride	50	1–2	50–100	4

^aNo neonatal studies were available at time of publication; the displayed details of dosing were obtained from studies on animals and in adult patients (Spragg et al. 2004; Hilgendorff et al. 2006)

been emphasized by Jobe (2006), who points out that there are 20 generations of airway branching from the trachea to the respiratory bronchioles and saccules, with 250,000 binary branch points and 500,000 distal airways leading to saccules. If the distribution is not proportionate to the number of saccules beyond each branch point, surfactant distribution will not be uniform. Any

nonuniformity at a proximal branch point will be amplified at subsequent branch points. When exogenous surfactant is administered in clinical practice, its distribution is not ideal, but is often good enough because of the biophysical properties of surfactant and the small amount that is needed regionally in the lung for a treatment response (Jobe 2006).

There are several variables that contribute to the distribution of surfactant in the lungs (Jobe 2006): surface activity causes rapid adsorption and spreading, gravity contributes to the distribution of surfactant in large airways, a higher volume of surfactant and faster administration cause better distribution, positive pressure ventilation and positive end-expiratory pressure help clear the airways of fluid, and higher volumes of fetal lung fluid or edema fluid improve distribution. Therefore techniques to improve surfactant distribution include positioning the infant to minimize gravity, giving surfactant quickly in a reasonable volume, and giving the infant enough ventilator support to quickly clear the airways of fluid.

According to the manufacturers' recommendations, beractant and poractant should be administered through a catheter inserted into the endotracheal tube, colfosceril should be administered through a side-port adapter attached to the endotracheal tube, and calf lung surfactant extract can be administered either through a feeding catheter or through a side-port adapter. Other methods of administration of surfactant have been tested in randomized trials as well and are described below.

Administration Through Catheter, Side Port, or Suction Valve: In a randomized trial, the administration of beractant through a catheter inserted through a neonatal suction valve without detachment of the neonate from the ventilator was compared to the administration of the dose (with detachment from the ventilator) in two aliquots through a catheter and to the standard technique of administration of the dose in four aliquots through a catheter (Zola et al. 1993a). Administration through the suction valve led to less dosing-related oxygen desaturation but more reflux of beractant than the two aliquot catheter technique. In another study (Soler et al. 1997), the administration of poractant as a bolus was compared in a randomized trial to administration via a catheter introduced through a side hole in the tracheal tube adaptor without changing the infants' position or interrupting ventilation. The numbers of episodes of hypoxia and/or bradycardia as well as other outcomes were similar in

both groups. A slight and transient increase in PaCO₂ was observed in the side-hole group.

Administration Through Dual-Lumen Endotracheal Tube: The administration of poractant through a dual-lumen endotracheal tube without a change in position or interruption of mechanical ventilation was compared to bolus instillation in a randomized trial (Soler et al. 1998). The dual-lumen group had fewer episodes of dosing-related hypoxia, a smaller decrease in heart rate and SaO₂, and a shorter total time in supplemental oxygen than the bolus group. The dual-lumen method has also been compared to the side-port method of administration of colfosceril in a randomized trial (Nelson et al. 1997). No difference was found between the two methods in dosing-related hypoxemia.

Slow Infusion Versus Bolus Administration: In one randomized clinical trial (Sitler et al. 1993), the slow infusion of colfosceril using a microinfusion syringe pump over 10–20 min was compared to manual instillation over 2 min. Pump administration resulted in fewer infants with loss of chest wall movement during dosing as well as a lesser increase in peak inspiratory pressure than with hand administration. In another small clinical trial of preterm infants (Zola et al. 1993b), there were no differences in clinical outcomes with administration by bolus *versus* slow infusion. However in animals, slow infusion of surfactant into the endotracheal tube results in nonhomogeneous distribution of surfactant in the lung (Ueda et al. 1994; Segerer et al. 1993). Because the evidence about the best method of administration is scant, and because bolus administration is likely to lead to better distribution, bolus administration of surfactant is preferred.

Other Methods: Other methods of administration such as nebulization or aerosolization (Berggren et al. 2000; Dijk et al. 1998; Ellyett et al. 1996; Fok et al. 1998; Jorch et al. 1997) and in utero administration to the human fetus (Cosmi et al. 1996; Petrikovsky et al. 1995) have also been reported. These methods require further clinical testing and are not currently recommended.

Chest Position During Administration of Surfactant: In a study in rabbits, pulmonary

distribution of intratracheally instilled surfactant was largely determined by gravity, and changing the chest position after instillation did not result in any redistribution of the surfactant. Therefore, for neonates receiving surfactant, keeping the chest in the horizontal position may result in the most even distribution of the surfactant in the two lungs (Broadbent et al. 1995).

In summary, based on available evidence, surfactant should be administered in the standard method of aliquots instilled into an endotracheal tube. There is evidence to suggest that the administration of surfactant using a dual-lumen endotracheal tube or through a catheter passed through a suction valve is effective and may cause less dosing-related adverse events than standard methods. The side-port method of administration and the catheter method of administration appear to be equivalent. More studies are required before firm conclusions can be drawn about the optimal method of administration of surfactant and whether the optimal method is different for different types of surfactant.

28.1.3.3 Clinical Use of Surfactant Therapy in Preterm Infants with RDS

Exogenous surfactant therapy is one of the best-studied therapies in neonatology and numerous randomized controlled trials have been performed comparing various treatment regimens and strategies. The findings from these trials, many of which are summarized in multiple systematic reviews in the Cochrane Database of Systematic Reviews (Sinclair et al. 2003), are described in the following sections. The results of the meta-analysis in these reviews are expressed as typical relative risk (RR) and typical absolute risk difference (ARD), with 95 % confidence intervals (CI) for each of these.

It is useful to clarify the terminology used for various treatment strategies with surfactant.

Prophylactic surfactant therapy: Administration of exogenous surfactant immediately after birth to an infant who is at risk of developing RDS, but may or may not already have clinical features of RDS.

Rescue (or selective) surfactant therapy: Administration of exogenous surfactant to an infant who has already developed clinical features of RDS.

Many clinical trials in the late 1980s and early 1990s studied the effects of rescue and prophylactic surfactant therapy compared to placebo or no therapy. Systematic reviews of these trials show that, compared to placebo or no therapy, surfactant treatment or prophylaxis (with either animal-derived or synthetic surfactant) decreases the risk of pneumothorax and of mortality. Estimates from the meta-analyses indicate that there is a 30–65 % relative reduction in the risk of pneumothorax and up to a 40 % relative reduction in the risk of mortality. There were no consistent effects on other clinical outcomes such as chronic lung disease, patent ductus arteriosus, and intraventricular hemorrhage.

Further evidence of the benefits of surfactant therapy is derived from studies demonstrating decreased mortality and morbidity in very low birth weight infants following the introduction of surfactant therapy into practice (Schwartz et al. 1994; Lee et al. 1999; Philip 1995; Doyle et al. 1999; Hamvas et al. 1996; Horbar et al. 1993a; Hoekstra et al. 1994).

28.1.3.3.1 Efficacy of Surfactant Therapy in Established RDS (Rescue Surfactant Therapy)

Many of the early surfactant trials studied the effects of surfactant treatment in preterm infants with clinical and/or radiologic features of RDS (rescue or treatment trials). Some of these studies used animal-derived surfactant and others used protein-free synthetic surfactant.

Rescue Therapy with Animal-Derived Surfactant: In a systematic review and meta-analysis of 13 randomized trials of animal-derived surfactant (Seger and Soll 2009), infants treated with surfactant had a rapid improvement in respiratory status (improved oxygenation and decreased need for ventilator support), as well as a significant decrease in the risk of (a) any air leak (typical RR 0.47, 95 % CI 0.39–0.58; typical ARD –0.16, 95 % CI –0.21 to –0.12), (b) pneumothorax (typical RR 0.42, 95 % CI

0.34–0.52; typical ARD -0.17 , 95 % CI -0.21 to -0.13), and (c) pulmonary interstitial emphysema (typical RR 0.45, 95 % CI 0.37–0.55; typical ARD -0.20 , 95 % CI -0.25 to -0.15). There was also a significant decrease in the risk of (a) neonatal mortality (typical RR 0.68, 95 % CI 0.57–0.82; typical ARD -0.09 , 95 % CI -0.13 to -0.05), (b) mortality prior to hospital discharge (typical RR 0.63, 95 % CI 0.44–0.90; typical ARD -0.10 , 95 % CI -0.18 to -0.03), and (c) bronchopulmonary dysplasia (BPD) or death at 28 days of age (typical RR 0.83, 95 % CI 0.77–0.90; typical ARD -0.11 , 95 % CI -0.16 to -0.06).

Rescue Therapy with Protein-Free Synthetic Surfactant: In a similar systematic review and meta-analysis of six randomized trials of protein-free synthetic surfactant treatment of established RDS (Soll 1998), surfactant therapy improved pulmonary gas exchange and decreased the requirement for ventilatory support. It also decreased the risk of (a) pneumothorax (typical RR 0.64, 95 % CI 0.55–0.76; typical ARD -0.09 , 95 % CI -0.12 to -0.06), (b) pulmonary interstitial emphysema (typical RR 0.62, 95 % CI 0.54–0.71; typical ARD -0.12 , 95 % CI -0.16 to -0.09), (c) patent ductus arteriosus (typical RR 0.90, 95 % CI 0.84–0.97; typical ARD -0.06 , 95 % CI -0.10 to -0.02), (d) intraventricular hemorrhage (typical RR 0.88, 95 % CI 0.77–0.99; typical ARD -0.04 , 95 % CI -0.08 to -0.00), (e) bronchopulmonary dysplasia (typical RR 0.75, 95 % CI 0.61–0.92; typical ARD -0.04 , 95 % CI -0.06 to -0.01), (f) neonatal mortality (typical RR 0.73, 95 % CI 0.61–0.88; typical ARD -0.05 , 95 % CI -0.07 to -0.02), (g) bronchopulmonary dysplasia or death at 28 days (typical RR 0.73, 95 % CI 0.65–0.83; typical ARD -0.06 , 95 % CI -0.11 to -0.05), (h) mortality prior to hospital discharge (typical RR 0.79, 95 % CI 0.68–0.92; typical ARD -0.05 , 95 % CI -0.07 to -0.02), and (i) mortality during the first year of life (typical RR 0.80, 95 % CI 0.69–0.94; typical ARD -0.04 , 95 % CI -0.07 to -0.01). Treatment with synthetic surfactant increased the risk of apnea of prematurity (typical RR 1.20, 95 % CI 1.09–1.31; typical ARD 0.08, 95 % CI 0.04–0.12).

28.1.3.3.2 Efficacy of Surfactant Therapy in Infants at Risk for RDS (Prophylactic Surfactant)

Several of the early trials of surfactant therapy also studied the effects of prophylactic surfactant in preterm infants at risk for developing RDS (i.e., before they had overt clinical features of RDS). Some of these studies used animal-derived surfactant and others used protein-free synthetic surfactant.

Prophylaxis with Animal-Derived Surfactant: A systematic review and meta-analysis of eight randomized trials (Soll and Özek 1997) found that prophylaxis with animal-derived surfactant lead to an initial improvement in respiratory status and a decrease in the risk of respiratory distress syndrome in infants. It also lead to a decrease in the risk of (a) pneumothorax (typical RR 0.35, 95 % CI 0.26–0.49; typical ARD -0.15 , 95 % CI -0.20 to -0.11), (b) pulmonary interstitial emphysema (typical RR 0.46, 95 % CI 0.35–0.60; typical ARD -0.19 , 95 % CI -0.25 to -0.13), (c) neonatal mortality (typical RR 0.60, 95 % CI 0.44–0.83; typical ARD -0.07 , 95 % CI -0.12 to -0.03), and (d) bronchopulmonary dysplasia or death (typical RR 0.84, 95 % CI 0.75–0.93; typical ARD -0.10 , 95 % CI -0.16 to -0.04).

Prophylaxis with Protein-Free Synthetic Surfactant: In a similar systematic review and meta-analysis of seven randomized trials (Soll and Özek 2010), protein-free synthetic surfactant prophylaxis leads to a variable improvement in the respiratory status and a decrease in respiratory distress syndrome in infants who receive prophylactic protein-free synthetic surfactant. It also leads to a decrease in the risk of (a) pneumothorax (typical RR 0.67, 95 % CI 0.50–0.90), (b) pulmonary interstitial emphysema (typical RR 0.68, 95 % CI 0.50–0.93), and (c) neonatal mortality (typical RR 0.70, 95 % CI 0.58–0.85). However, prophylactic protein-free synthetic surfactant administration was associated with an increase in the risk of patent ductus arteriosus (typical RR 1.11, 95 % CI 1.00–1.22) and an increase in the risk of pulmonary hemorrhage (typical RR 3.28, 95 % CI 1.50–7.16).

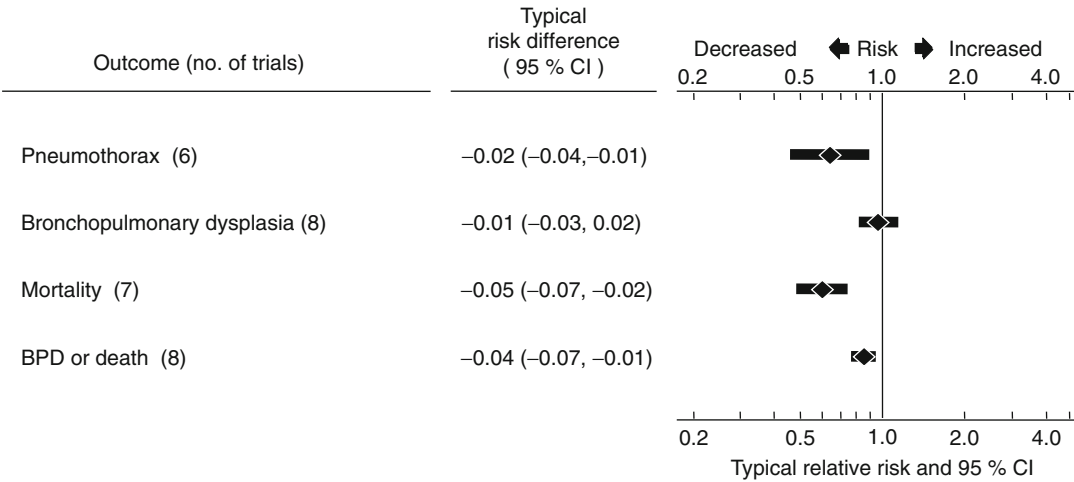


Fig. 28.2 Meta-analysis of eight randomized controlled trials comparing surfactant prophylaxis and treatment (Soll 2001)

28.1.3.3.3 Prophylactic Versus Rescue Surfactant Therapy

Many investigators believed that prophylactic administration of surfactant would be the most effective way to deliver surfactant based on the observation in animal studies that surfactant is distributed more uniformly and homogenously when it is administered into a fluid-filled lung (Jobe et al. 1984; Seidner et al. 1995) and the belief that administering surfactant into a previously unventilated or minimally ventilated lung will diminish acute lung injury. In animal models, even brief (15–30 min) periods of mechanical ventilation prior to surfactant administration have been shown to cause acute lung injury resulting in alveolar–capillary damage, leakage of proteinaceous fluid into the alveolar space, and release of inflammatory mediators (Ikegami et al. 1998; Jobe and Ikegami 1998a, b) and to decrease the subsequent response to surfactant replacement (Bjorklund et al. 1997; Rider et al. 1992). Surfactant-deficient animals who receive assisted ventilation develop necrosis and desquamation of the bronchiolar epithelium as early as 5 min after onset of ventilation (Nilsson et al. 1980).

Shortly after surfactant was approved for clinical use, eight randomized controlled trials compared the effects of prophylactic surfactant administration to surfactant treatment of established RDS (Bevilacqua et al. 1996, 1997;

Dunn et al. 1991; Egberts et al. 1993; Kattwinkel et al. 1993; Kendig et al. 1991; Merritt et al. 1991; Walti et al. 1995). All these trials used animal-derived surfactant preparations. Trials varied whether surfactant was given before or after the onset of air breathing (pre- or post-ventilatory administration), but all administered surfactant before 15 min of age. The average time of administration of surfactant in the selective treatment groups ranged from 1.5 to 7.4 h. The results of the meta-analysis of the eight trials from a systematic review (Soll and Morley 2012) are summarized in Fig. 28.2.

Compared to surfactant treatment of established RDS, prophylactic administration of surfactant resulted in a decrease in the risk of pneumothorax (typical RR 0.62, 95 % CI 0.42–0.89; typical ARD -0.02, 95 % CI -0.04 to -0.01), a decrease in the risk of pulmonary interstitial emphysema (typical RR 0.54, 95 % CI 0.36–0.82; typical ARD -0.03, 95 % CI -0.04 to -0.01), a reduction in the risk of neonatal mortality (typical RR 0.61, 95 % CI 0.48–0.77; typical ARD -0.05, 95 % CI -0.07 to -0.02), and a trend towards a decrease in the risk of intraventricular hemorrhage (typical RR 0.92, 95 % CI 0.82–1.03; typical ARD -0.03, 95 % CI -0.06 to 0.01). Because of the greater risk of respiratory distress syndrome and mortality with decreasing gestational age, the benefits of

prophylactic administration compared to selective administration were of greater magnitude. The meta-analysis demonstrates that compared to selective administration, prophylactic administration of animal-derived surfactant to infants less than 30 weeks gestation resulted in a greater reduction in neonatal mortality (typical RR 0.62, 95 % CI 0.49–0.78; typical ARD –0.06, 95 % CI –0.09 to –0.03) and a reduction in the combined outcome of bronchopulmonary dysplasia or death (typical RR 0.87, 95 % CI 0.77–0.97; typical ARD –0.05, 95 % CI –0.09 to –0.01).

Preventilatory Versus Post-ventilatory Prophylactic Surfactant Administration: The initial studies using prophylactic surfactant administered the drug as an immediate bolus after intubating the infants rapidly after birth (i.e., “before the first breath”). This approach delays the initiation of neonatal resuscitation, including positive pressure ventilation, and is associated with a risk for surfactant delivery into the right main stem bronchus or esophagus. A randomized trial demonstrated that prophylaxis may be administered in small aliquots soon after resuscitation and confirmation of endotracheal tube position, with equivalent or greater efficacy (Kendig et al. 1998). Based on this trial, prophylactic surfactant should be administered after initial resuscitation of the infant at birth and administration prior to the “first breath” is unnecessary.

The trials mentioned above comparing the use of prophylactic surfactant to surfactant treatment of established RDS were all performed in an era when the use of maternal antenatal glucocorticoids was not as high as in the current era, where 90 % or more of mothers who deliver prematurely receive antenatal glucocorticoids. Also, in these trials, surfactant in the “rescue” group was given relatively late, between 1.5 and 7.4 h, after birth. There are no trials comparing the effects of prophylactic intubation and surfactant administration shortly after birth to infants at high risk of RDS (with intubation primarily performed to administer surfactant) to very early selective administration (e.g., at 30–60 min of life) in intubated infants with early RDS or respiratory insufficiency. Therefore, in current practice, the benefits of prophylactic surfactant demonstrated

in these trials might not be as large. A strategy of surfactant prophylaxis subjects infants without RDS to unnecessary intubation and surfactant administration and also to the risk of ventilator-induced lung injury (Clark et al. 2001) (although admittedly some of these infants without RDS may still require intubation and ventilation for respiratory failure not due to RDS). In recent years, prophylactic surfactant administration to preterm infants at risk of RDS has been compared with the use of nasal CPAP (and attempting to avoid mechanical ventilation) as the primary method of respiratory management at birth. These studies are discussed in the next section.

28.1.3.3.4 Initial Respiratory Management of Preterm Infants: CPAP Compared to Intubation Followed by Surfactant Administration

Four large multicenter trials have evaluated the use of prophylactic or early surfactant administration to immediate stabilization on continuous distending pressure (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network 2010; Vermont Oxford Network DRM Study Group et al. 2010; Sandri et al. 2010; Morley et al. 2008).

In the SUPPORT trial (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network 2010), infants 24–27 weeks gestation were randomly assigned to intubation and surfactant treatment (within 1 h after birth) or to CPAP treatment initiated in the delivery room, with subsequent use of a “protocol-driven limited ventilation strategy.” The primary outcome, death, or bronchopulmonary dysplasia (defined as supplemental oxygen requirement at 36 weeks post-menstrual age) did not differ significantly between the CPAP group and the surfactant group (47.8 and 51.0 %, respectively; RR with CPAP, 0.95; 95 % CI, 0.85–1.05) after adjustment for gestational age, center, and familial clustering. The results were similar when bronchopulmonary dysplasia was defined according to the need for any supplemental oxygen at 36 weeks (rates of primary outcome, 48.7 and 54.1 %, respectively; RR with CPAP, 0.91; 95 %

CI, 0.83–1.01). Infants who received CPAP treatment, as compared with infants who received surfactant treatment, less frequently required intubation or postnatal corticosteroids for bronchopulmonary dysplasia ($P<0.001$), required fewer days of mechanical ventilation ($P=0.03$), and were more likely to be alive and free from the need for mechanical ventilation by day 7 ($P=0.01$). In secondary analyses, among infants 24 and 25 weeks gestation, there was a significant reduction in the risk of death in the CPAP group, as compared with the early-intubation group. The rate of death during hospitalization was 24 % *versus* 32 %, RR with CPAP, 0.74; 95 % CI 0.57–0.98. The rate of death at 36 weeks was 20 % *versus* 29 %, RR, 0.68; 95 % CI 0.5–0.92.

In the Delivery Room Management randomized trial conducted by the Vermont Oxford Network (Vermont Oxford Network DRM Study Group et al. 2010), three strategies were compared in infants at risk of RDS (preterm infants 26–29 weeks): prophylactic surfactant followed by a period of assisted ventilation, intubation with immediate surfactant treatment and rapid extubation to nasal CPAP (ISX), and early stabilization on nasal CPAP (NCPAP). The study was terminated prior to reaching the desired sample size. There were over 200 infants in each of the three study arms. No statistically significant differences were found between the three arms of the trial in the primary outcome of death or chronic lung disease (defined as supplemental oxygen requirement at 36 weeks post-menstrual age). The incidence of the primary outcome was 37 % in the prophylactic surfactant group, 29 % in the ISX group (RR with ISX compared to prophylactic surfactant 0.78, 95 % CI 0.59–1.03), and 31 % in the CPAP group (RR with CPAP compared to prophylactic surfactant 0.83, 95 % CI 0.64–1.09).

In the CURPAP trial (Sandri et al. 2010), infants 25–28 weeks gestation who were not intubated at birth were randomly assigned to prophylactic surfactant or nasal CPAP within 30 min of birth. There were no statistically significant differences between the two groups in the outcomes studied – need for mechanical ventilation in the first 5 days of life, death at

28 days of life, death at 36 weeks post-menstrual age, and the main morbidities of prematurity.

In the COIN trial (Morley et al. 2008), infants 25–28 weeks gestation who were breathing spontaneously but had developed respiratory distress were randomly assigned to CPAP or intubation and ventilation at 5 min after birth. Infants intubated before randomization and those not requiring respiratory support or oxygen were excluded. The primary outcome of death or chronic lung disease (defined as the need for oxygen treatment at 36 weeks gestational age) was not statistically different in infants assigned to receive intubation (39 %) compared with infants assigned to receive CPAP (34 %, odds ratio favoring CPAP, 0.80; 95 % CI 0.58–1.12). At 28 days, there was a lower risk of death or need for oxygen therapy in the CPAP group than in the intubation group (odds ratio, 0.63; 95 % CI 0.46–0.88; $P=0.006$). There was little difference in overall mortality. In the CPAP group, 46 % of infants were intubated during the first 5 days, and the use of surfactant was halved. However, the incidence of pneumothorax was 9 % in the CPAP group, as compared with 3 % in the intubation group ($P<0.001$). There were no other serious adverse events. The CPAP group had fewer days of ventilation.

The results of these trials suggest that in preterm infants at high risk of RDS, instead of routinely intubating and administering prophylactic surfactant immediately after birth, it is reasonable to try and initially stabilize such infants on nasal CPAP. This approach can avoid unnecessary intubation, unnecessary surfactant administration, and minimize ventilator-induced lung injury, while reducing healthcare costs and resource utilization. However, clinicians should closely monitor infants initially stabilized on CPAP to identify infants who have progressive respiratory failure, so that infants who require surfactant can be intubated and given surfactant as early as possible. Clinicians should also use information available prior to the birth of the infant to identify infants who are not likely to do well with initial stabilization on nasal CPAP, such as infants born to mothers who have not received antenatal glucocorticoids.

28.1.3.3.5 The Preterm Infant with Respiratory Distress Syndrome Who Is Not on Mechanical Ventilation

When a preterm infant has respiratory distress syndrome that is initially managed with CPAP or with supplemental oxygen through a hood, is it better to intubate him early, administer surfactant and extubate within an hour after brief mechanical ventilation, or to wait and see if the infant develops significant respiratory insufficiency, and if he does, only then intubate, give surfactant, and wean him off the ventilator gradually? Six randomized controlled clinical trials addressed this question and are summarized in a systematic review (Stevens Timothy et al. 2007). The rapid (within one hour) extubation attempted in these trials contrasts with the traditional approach – developed when surfactant therapy was first used – of keeping an infant on mechanical ventilation after surfactant administration, weaning ventilator support gradually as the pulmonary status improved, and extubating the infant from low ventilator settings. This approach of rapid extubation followed immediately by the use of nasal CPAP has been called “INSURE” (INtubate, SURfactant, Extubate to CPAP) and is intended to prevent ventilator-induced lung injury than can result from even brief periods of mechanical ventilation (Donn and Sinha 2006; Schmolzer et al. 2008). The six randomized trials, all of which are trials of “rescue” surfactant administration, are summarized in a systematic review (Stevens Timothy et al. 2007). Most of these studies included infants with a gestation of 35 weeks and below and a birth weight of 2,500 g and below. Many of the infants in these studies were between 32 and 35 weeks (few were extremely premature). In these studies of infants with signs and symptoms of RDS, intubation and early surfactant therapy followed by extubation to nasal CPAP (NCPAP) compared with later selective surfactant administration was associated with a lower incidence of mechanical ventilation (typical RR 0.67, 95 % CI 0.57–0.79; typical ARD –0.19, 95 % CI –0.26 to –0.11), air leak syndromes (typical RR 0.52, 95 % CI 0.28–0.96; typical ARD –0.04, 95 % CI –0.08 to 0.00),

and BPD (typical RR 0.51, 95 % CI 0.26–0.99; typical ARD –0.08, 95 % CI –0.15 to –0.01). A larger proportion of infants in the early surfactant group received surfactant than in the selective surfactant group (typical RR 1.62, 95 % CI 1.41–1.86; typical ARD 0.38, 95 % CI 0.30–0.47). The number of surfactant doses per patient was significantly greater among patients randomized to the early surfactant group (WMD 0.57 doses per patient, 95 % CI 0.44–0.69). In stratified analysis by FiO_2 at study entry, a lower threshold for treatment ($\text{FiO}_2 \leq 0.45$) resulted in lower incidence of air leak (typical RR 0.46 and 95 % CI 0.23–0.93; typical ARD –0.05, 95 % CI –0.10 to –0.01) and BPD (typical RR 0.43, 95 % CI 0.20–0.92; typical ARD –0.10, 95 % CI –0.19 to –0.02). A higher treatment threshold ($\text{FiO}_2 > 0.45$) at study entry was associated with a higher incidence of patent ductus arteriosus requiring treatment (typical RR 2.15, 95 % CI 1.09–4.13; typical ARD 0.12, 95 % CI 0.02–0.21). In another recent randomized trial (Rojas et al. 2009), infants 27–31 weeks gestation with RDS who were randomly assigned within the first hour of life either to intubation, very early surfactant, extubation, and nasal continuous positive airway pressure required less ventilation and had a lower incidence of mortality and air leaks (pneumothorax and pulmonary interstitial emphysema) than infants assigned to nasal continuous airway pressure alone. These data suggest that for a preterm infant with RDS who is not on mechanical ventilation (and is being managed on CPAP or an oxygen hood), early intubation at a low FiO_2 threshold ($\text{FiO}_2 < 0.45$), surfactant administration, and rapid extubation to CPAP decreases the risk of needing mechanical ventilation, BPD, and air leak syndrome, although it results in more surfactant use. Whether the same INSURE approach should be followed when prophylactic surfactant therapy is used is not clear due to lack of evidence.

28.1.3.3.6 Early Versus Late Treatment of Established RDS

Preterm infants who do not receive prophylaxis and subsequently develop RDS should be treated with surfactant as soon as possible. This strategy

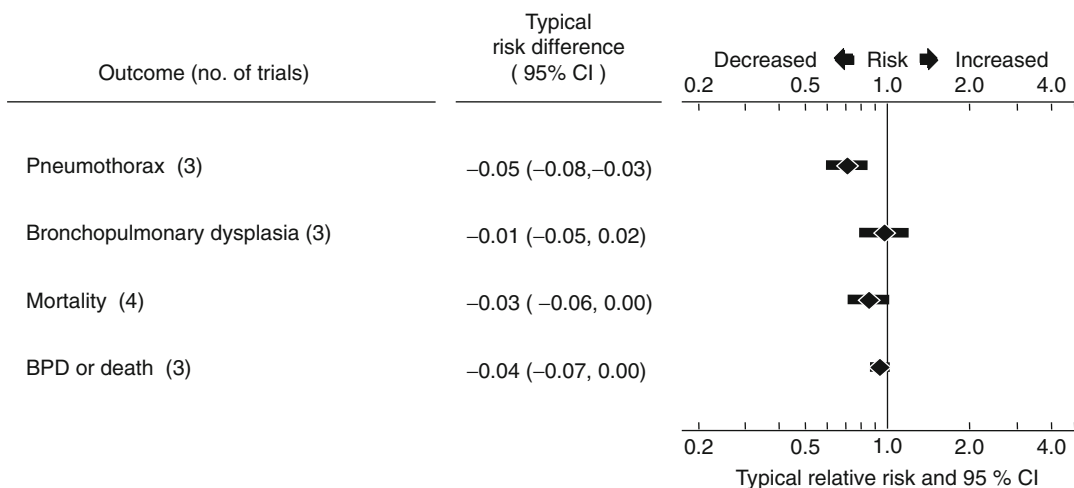


Fig. 28.3 Meta-analysis of four randomized controlled trials comparing early and delayed surfactant treatment (Yost and Soll 2000)

is supported by many of the same arguments that support prophylactic surfactant administration as well as by clinical trials. Four randomized controlled trials (European Exosurf Study Group 1992; Gortner et al. 1998; Konishi et al. 1992; The OSIRIS Collaborative Group 1992), including the largest randomized trial conducted in neonatology (the OSIRIS trial), have evaluated early *versus* delayed selective surfactant administration. The results of these trials are summarized in a systematic review (Yost and Soll 2000). In these trials, early administration of surfactant consisted of administration of the first dose within the first 30 min to the first 2 h of life. Two of these studies used animal-derived surfactants and two used protein-free synthetic surfactant. The results of the meta-analysis of these studies are summarized in Fig. 28.3.

Early selective treatment resulted in a decrease in the risk of pneumothorax (typical RR 0.70, 95 % CI 0.59–0.82; typical ARD -0.05, 95 % CI -0.08 to -0.03), a decrease in the risk of pulmonary interstitial emphysema (typical RR 0.63, 95 % CI 0.43–0.93; typical ARD -0.06, 95 % CI -0.10 to -0.01), a decrease in the risk of chronic lung disease (requirement for supplemental oxygen at 36 weeks gestation, typical RR 0.70, 95 % CI 0.55–0.88; typical ARD -0.03, 95 % CI -0.05 to -0.01) and a decrease in the risk of neonatal mortality (typical RR 0.87, 95 % CI 0.77–0.99;

typical ARD -0.03, 95 % CI -0.06 to 0.00). Therefore preterm infants who do not receive prophylactic surfactant and subsequently develop clinical features of RDS should receive the first dose of surfactant as early as possible. Outborn infants are at highest risk of delayed administration. Tertiary referral units accepting outborn infants should attempt to develop systems to ensure that surfactant is administered as early as possible to these infants, either by the transporting team or, if appropriate, by the referring hospital. In inborn infants, delays in administration of surfactant occur if other admission procedures such as line placement, radiographs, and nursing procedures are allowed to take precedence over surfactant dosing soon after birth. Surfactant administration should be given priority over such admission procedures.

28.1.3.3.7 Single Versus Multiple Surfactant Doses

Many of the initial trials of surfactant therapy tested a single dose of surfactant. However, surfactant may become rapidly metabolized and functional inactivation of surfactant can result from the action of soluble proteins and other factors in the small airways and alveoli (Jobe and Ikegami 1993). Administering repeat doses of surfactant can overcome such inactivation. The results of two randomized controlled trials

that compared multiple dosing regimens to single-dose regimens of animal-derived surfactant extract for treatment of established respiratory distress syndrome (Dunn et al. 1990; Speer et al. 1992) have been evaluated in a systematic review (Soll and Özek 2009). In one study (Dunn et al. 1990), after the initial dose of bovine lipid extract surfactant, infants assigned to the multiple-dose group could receive up to three additional doses during the first 72 h of life if they had a respiratory deterioration, provided they had shown a positive response to the first dose and a pneumothorax had been eliminated as the cause of the respiratory deterioration. In the other study (Speer et al. 1992), infants in the multiple-dose group received additional doses of poractant at 12 and 24 h after the initial dose if they still needed supplemental oxygen and mechanical ventilation. Approximately 70 % of the infants randomized to the multiple-dose regimen received multiple doses.

The meta-analysis supports a decreased risk of pneumothorax associated with multiple dose surfactant therapy (typical RR 0.51, 95 % CI 0.30–0.88; typical ARD –0.09, 95 % CI –0.15 to –0.02). There was also a trend towards decreased mortality (typical RR 0.63, 95 % CI 0.39–1.02; typical ARD –0.07, 95 % CI –0.14 to 0.00). No differences were detected in other clinical outcomes. No complications associated with multiple-dose treatment were reported in these trials. In a third study, in which protein-free synthetic surfactant was used in a prophylactic manner, the use of two doses of surfactant in addition to a prophylactic dose lead to a decrease in mortality, respiratory support, necrotizing enterocolitis, and other outcomes when compared to a single prophylactic dose (Corbet et al. 1995). In the OSIRIS trial, which used protein-free synthetic surfactant, a two-dose treatment schedule was found to be equivalent to a treatment schedule permitting up to four doses of surfactant.

28.1.3.3.8 Threshold for Administration of Repeat Doses of Surfactant

The use of a higher threshold for retreatment with surfactant appears to be as effective as a low threshold and can lead to significant savings in

costs of the drug. The criteria for administration of repeat doses of surfactant were investigated in two studies that both used animal-derived surfactant. In one study (Dunn et al. 1991), the retreatment criteria compared were an increase in the fraction of inspired oxygen by 0.1 over the lowest baseline value (standard retreatment) *versus* a sustained increase of just 0.01 (liberal retreatment). There were no differences in complications of prematurity or duration of respiratory support. However, short-term benefits in oxygen requirement and degree of ventilator support were noted in the liberal retreatment group.

In another study (Kattwinkel et al. 2000), retreatment at a low threshold ($\text{FiO}_2 > 30$ %, still requiring endotracheal intubation) was compared to retreatment at a high threshold ($\text{FiO}_2 > 40$ %, mean airway pressure > 7 cm H_2O). Again, there were minor short-term benefits to using a low threshold with no differences in major clinical outcomes. However, in a subgroup of infants with respiratory distress syndrome complicated by perinatal compromise or infection, infants in the high-threshold group had a trend towards higher mortality than the low-threshold group. Based on current evidence, it appears appropriate to use persistent or worsening signs of respiratory distress syndrome as criteria for retreatment with surfactant. A low threshold for repeat dosing should be used for infants with RDS who have perinatal depression or infection.

28.1.3.3.9 Comparisons Between Surfactant Products

Comparison of Animal-Derived and Protein-Free Synthetic Surfactants: Although both protein-free synthetic and animal-derived surfactants are effective, their composition differs. Animal-derived surfactant extracts contain surfactant-specific proteins that aid in surfactant adsorption and resist surfactant inactivation (Kuroki and Voelker 1994; Possmayer 1990). Eleven randomized trials have compared the effects of animal-derived and protein-free synthetic surfactants in the treatment or prevention of RDS (Ainsworth et al. 2000; Alvarado et al. 1993; da Costa et al. 1999; Horbar et al. 1993b; Hudak et al. 1996, 1997; Kukkonen et al. 2000;

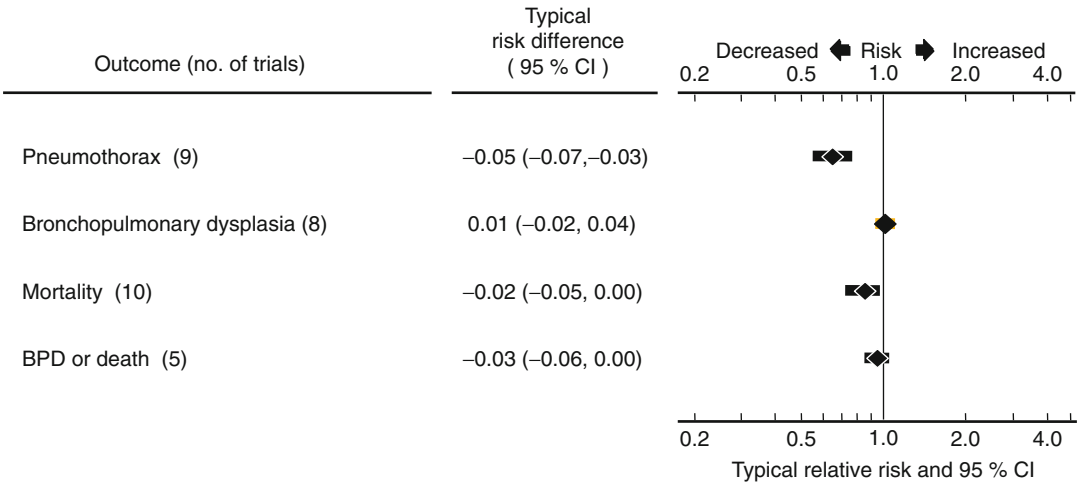


Fig. 28.4 Meta-analysis of 11 randomized controlled trials comparing animal-derived and synthetic surfactants (Soll 2001)

Modanlou et al. 1997; Pearlman et al. 1993; Sehgal et al. 1994; Neonatal 1996). A total of over 4,500 infants were studied in these trials. A systematic review of these trials is available (Soll and Blanco 2001). The results of the meta-analysis are summarized in Fig. 28.4.

Compared to protein-free synthetic surfactant, treatment with animal-derived surfactant extracts resulted in a significant reduction in the risk of pneumothorax (typical RR 0.63, 95 % CI 0.53–0.75; typical ARD -0.04, 95 % CI -0.06 to -0.03) and the risk of mortality (typical RR 0.87, 95 % CI 0.76–0.98; typical ARD -0.02, 95 % CI -0.05 to 0.00). Natural surfactant extract is associated with a marginal increase in the risk of intraventricular hemorrhage (typical RR 1.09, 95 % CI 1.00–1.19; typical ARD 0.03, 95 % CI 0.00–0.06), but no increase in grade 3 to 4 intraventricular hemorrhage (typical RR 1.08, 95 % CI 0.92–1.28; typical ARD 0.01, 95 % CI -0.01 to 0.03). The meta-analysis also supports a marginal decrease in the risk of bronchopulmonary dysplasia or mortality associated with the use of natural surfactant preparations (typical RR 0.95, 95 % CI 0.90–1.01; typical ARD -0.03, 95 % CI -0.06 to 0.00).

In addition to these benefits, animal-derived surfactants have a more rapid onset of action, allowing ventilator settings and inspired oxygen concentrations to be lowered more quickly than

with protein-free synthetic surfactant (Horbar et al. 1993b; Hudak et al. 1996; Modanlou et al. 1997; Rollins et al. 1993; Choukroun et al. 1994). A comparison of physical properties and the results of animal studies also suggest that animal-derived surfactants have advantages over protein-free synthetic surfactants (Halliday 1996). These properties are attributed to the presence of the surfactant proteins SP-B and SP-C in animal-derived surfactants (Hall et al. 1992a).

The use of animal-derived surfactant preparations should be favored in most clinical situations, as their use results in greater clinical benefits than protein-free synthetic surfactants. However, all animal-derived surfactants have to be refrigerated for storage. The protein-free synthetic surfactant colfosceril is available as a lyophilized powder that is to be stored at below 30 °C in a dry place (not to be frozen) and reconstituted with sterile water before use. Therefore in situations where refrigeration is a problem (as in developing countries), it may be more practical to use colfosceril than animal-derived surfactants.

Comparison of Animal-Derived and Protein-Containing Synthetic Surfactants: Clinical trials have compared the effects of synthetic surfactants containing peptides to animal-derived surfactant preparations. These synthetic surfactants do not have the theoretical concerns

associated with animal-derived surfactants, namely, transmission of microorganisms, exposure to animal proteins and inflammatory mediators, susceptibility to inactivation, and inconsistent content (Engle and Committee on Fetus and Newborn 2008). Lucinactant, the synthetic surfactant containing an analog of SP-B, sinapultide, was compared with beractant in SELECT, a multicenter masked randomized trial of surfactant prophylaxis in infants 24–32 weeks gestation (Moya et al. 2005). Lucinactant was also compared with poractant in STAR, a multicenter randomized trial of surfactant prophylaxis in infants 24–28 weeks gestation that was structured as a non-inferiority trial (Sinha et al. 2005). A meta-analysis of these two studies (Pfister et al. 2007) found no significant differences in outcomes between lucinactant and the comparison animal-derived surfactant in mortality at 36 weeks post-menstrual age (typical RR 0.81, 95 % CI 0.64–1.03), chronic lung disease at 36 weeks post-menstrual age (typical RR 0.99, 95 % CI 0.84–1.18), the composite outcome of mortality or chronic lung disease at 36 weeks post-menstrual age (typical RR 0.96, 95 % CI 0.82–1.12), or in other respiratory outcomes. A decreased risk of necrotizing enterocolitis, a secondary outcome, was noted in infants receiving lucinactant (typical RR 0.60, 95 % CI 0.42–0.86; typical RD –0.06, 95 % CI –0.10 to –0.01).

However, both trials of lucinactant described above had multiple methodologic problems (Kattwinkel 2005) that undermine their validity, and at present there is no clear evidence of the equivalence or superiority of lucinactant over any animal-derived surfactant product (Halliday 2006). While these newer surfactants show promise, further research is required to elucidate their role in the prevention or treatment of RDS.

Comparison of Protein-Containing Versus Protein-Free Synthetic Surfactants: In the SELECT trial (Moya et al. 2005; Pfister Robert et al. 2009), the randomized trial of lucinactant mentioned above where it was compared with beractant, it was also compared to colfosceril. Compared to infants receiving colfosceril, infants receiving lucinactant had less RDS (39 % vs 47 %) and less RDS-related mortality (4.7 % vs

9.4 %, RR 0.50, 95 % CI 0.32–0.80). All-cause mortality at 36 weeks post-menstrual age was not significantly different (21 % for lucinactant vs 24 % for colfosceril). A trend towards a reduction in BPD or death at 36 weeks post-menstrual age was associated with lucinactant treatment when compared to colfosceril (RR 0.88, 95 % CI 0.77–1.01).

Comparison of Different Types of Bovine Surfactants: Two randomized trials, both from the same group of investigators, have compared the efficacy and adverse effects of different bovine surfactant products. In a comparison of beractant (Survanta) and calf lung surfactant extract (Infasurf) (Bloom et al. 1997), there were no differences detected between the two groups in the frequency of air leaks, complications associated with dosing, complications of prematurity, mortality, or survival without chronic lung disease. However, some differences were noted among subgroups of infants. Among infants treated for established respiratory distress syndrome, those who received calf lung surfactant extract had a significantly longer interval between doses, a lower inspired oxygen concentration, and a lower mean airway pressure in the first 48 h of life than infants treated with beractant. Among infants in whom these surfactants were administered in a preventive manner, mortality in infants with a birth weight <600 g was significantly higher with calf lung surfactant extract than with beractant. In a second report (Bloom et al. 2005) that included two separate trials – a prophylaxis trial and a treatment trial – the trials were halted prematurely due to recruitment problems and hence had inconclusive results with no demonstrated differences in outcomes between the two products. Thus, there is no evidence of the superiority of one bovine preparation over the other.

Comparison of Porcine and Bovine Surfactants: Five studies comparing surfactant treatment of established moderate to severe RDS with poractant *versus* beractant have been published (Baroutis et al. 2003; Speer et al. 1995; Malloy et al. 2005; Halahakoon 1999; Ramanathan et al. 2004).

A meta-analysis of these studies (Halliday 2005) found that compared to beractant,

poractant treatment led to a significant reduction in neonatal mortality (typical RR 0.57, 95 % CI 0.34–0.96). The dose of beractant was uniformly 100 mg/kg across all five studies. When only studies that used a 100 mg/kg dose of poractant were considered, the reduction in mortality was not statistically significant (typical RR 0.82, 95 % CI 0.44–1.58), emphasizing the fact that the most significant effect on mortality was seen with a 200 mg/kg dose of poractant (typical RR 0.29, 95 % CI 0.10–0.79). Two of these five studies (Speer et al. 1995; Ramanathan et al. 2004) also reported more rapid improvement in oxygenation with poractant compared to beractant. The difference in outcomes described above between poractant and beractant may well be related to the dose of phospholipids and not to other characteristics of the products. There are no studies to determine whether poractant, especially in a 100 mg/kg dose, is superior to beractant when surfactant is dosed for prophylaxis.

28.1.3.3.10 Factors Affecting the Response to Surfactant Therapy

Several factors have been reported by various authors to be associated with a poor response to surfactant therapy, either in terms of immediate pulmonary response or in terms of later morbidity and mortality. These factors include high total fluid and colloid intake in the first days of life (Hallman et al. 1993), a low mean airway pressure relative to the FiO_2 (Hallman et al. 1993), the presence of an additional pulmonary disorder such as infection (Segerer et al. 1991) and perinatal asphyxia, other complications of prematurity (Konishi et al. 1992), high fraction of inspired oxygen requirement at entry (had a negative impact on a/APO_2 6 and 24 h after treatment), lower birth weight, male sex, outborn status, and high airway pressure requirement at entry (Collaborative European Multicentre Study Group 1991). Low birth weight, low Apgar score, and initial disease severity were associated with an increased mortality (Herting et al. 1992).

A high pulmonary resistance prior to therapy was associated with a poor response to therapy at 24 and 48 h (Wallenbrock et al. 1992). In

addition, the immediate response to surfactant therapy itself has been reported to be a significant prognostic indicator for mortality and morbidity (Kuint et al. 1994). In animal studies, poor response to surfactant has been associated with delayed administration (Seidner et al. 1995) and the leakage of proteinaceous fluid into the alveolar spaces. Within some multicenter trials, significant differences in outcomes of surfactant-treated infants have been noted between participating hospitals (Collaborative European Multicentre Study Group 1991; Herting et al. 1992), suggesting that variations in patient care practices have an important influence on the outcomes of surfactant-treated infants.

As noted earlier, observational studies have demonstrated a decrease in mortality and morbidity for such infants after the introduction of surfactant therapy. However, racial differences in this decline in mortality have been reported. In one study, the overall neonatal mortality for black very low birth weight infants did not change after the introduction of surfactant therapy (Hamvas et al. 1996), and in another study, declines in neonatal mortality risks caused by respiratory distress syndrome and all respiratory causes were greater for non-Hispanic white VLBW infants than for black VLBW infants (Ranganathan et al. 2000). While such racial differences have been noted at a population level, the role of racial factors in the response pattern of individual infants with respiratory distress syndrome to exogenous surfactant therapy is unknown.

28.1.3.4 Adverse Effects of Surfactant Therapy

Transient hypoxia and bradycardia can occur due to acute airway obstruction immediately following surfactant instillation (Zola et al. 1993a; Liechty et al. 1991). Other acute adverse effects of surfactant administration include reflux of surfactant into the pharynx from the endotracheal tube, increase in transcutaneous carbon dioxide tension, tachycardia, gagging, and mucous plugging of the endotracheal tube. These complications of surfactant administration generally respond to a slower rate of surfactant administration or to an increased airway pressure or FiO_2

during administration. Rapid improvement in oxygenation after surfactant administration necessitates close monitoring and appropriate reduction of ventilatory parameters.

Several authors have reported a transient decrease in blood pressure (Hellstrom-Westas et al. 1992; Skov et al. 1992a, b), a transient decrease in cerebral blood flow velocity (Cowan et al. 1991; Murdoch and Kempley 1998; Edwards et al. 1992), a transient decrease in cerebral oxyhemoglobin concentration (Edwards et al. 1992), and a transient decrease in cerebral activity on amplitude-integrated electroencephalography (Hellstrom-Westas et al. 1992) immediately after surfactant administration. The EEG depression observed after surfactant instillation is not caused by cerebral ischemia (Bell et al. 1994), and the EEG suppression is not directly related to alterations in blood gases or systemic circulation (Lundstrom and Greisen 1996). The clinical significance of these findings is uncertain. One study (Horbar et al. 1990) reported an increase in the incidence of intraventricular hemorrhage and a case report documents a temporal association between the development of intraventricular hemorrhage and the administration of surfactant-TA to improve respiratory failure caused by pulmonary hemorrhage (Funato et al. 1992). However, the meta-analyses of multiple trials do not show an increase in the risk of intraventricular hemorrhage with surfactant therapy compared to placebo (Seger and Soll 2009; Soll 1998; Soll and Özek 1997, 2010).

There is well-described increase in the risk of pulmonary hemorrhage with surfactant therapy (Raju and Langenberg 1993; Tomaszewska et al. 1999). Although trials in which animal-derived surfactants were used reported a higher incidence (5–6 %) of pulmonary hemorrhage than trials of protein-free synthetic surfactant (1–3 %), direct comparison demonstrates no difference in the risk of pulmonary hemorrhage. The overall incidence of pulmonary hemorrhage was low and the absolute magnitude of the increased risk is small (Raju and Langenberg 1993). However, moderate and severe pulmonary hemorrhage is associated with an increased risk of death and short-term morbidity. It is not associated with increased

long-term morbidity (Pandit et al. 1999). The occurrence of pulmonary hemorrhage may be related to the presence of a hemodynamically significant patent ductus arteriosus (Garland et al. 1994). Seppanen et al. studied the association of neonatal complications with the Doppler-derived aortopulmonary pressure gradient (APPG) across the ductus arteriosus, which reflects pulmonary artery pressure during the first day of life. Infants in whom the APPG decreased after birth had a lower frequency of patent ductus arteriosus and pulmonary hemorrhage than those whose APPG remained low (Seppanen et al. 1995). Another mechanism for the pulmonary hemorrhage may be a direct cytotoxicity, which has been demonstrated in *in vitro* studies and appears to be different for different surfactants and different dosages (Findlay et al. 1995).

When surfactant initially became available for clinical testing, there was concern that the introduction of foreign proteins from animal-based lung surfactants into the lungs of preterm infants could lead to immunological responses. Two studies did not find antibodies specific to surfactant protein in the sera of preterm infants treated with bovine surfactant (Bartmann et al. 1992; Whitsett et al. 1991). In other studies, immune complexes or antibodies to the protein in exogenous porcine, bovine, or human surfactant have been identified in the sera of neonates with respiratory distress syndrome. However similar immune complexes or antibodies were also noted in control infants who did not receive surfactant, and no significant differences were noted between surfactant-treated and control infants (Chida et al. 1991; Strayer et al. 1989; Robertson et al. 1992). The presence of antibodies in control infants may be the result of leakage of surfactant proteins into the circulation (Chida et al. 1991).

With animal-derived surfactants, there is a theoretical risk of the transmission of infectious agents, including bovine spongiform encephalitis with surfactants derived from bovine sources and other viral infections in swine. Organic solvent processing of phospholipids, terminal sterilization techniques, and screening of animal sources have been used to minimize this risk.

28.1.3.5 Long-Term Outcomes After Surfactant Therapy

Long-term outcomes after surfactant therapy have been well studied for protein-free synthetic surfactant. Follow-up studies of long-term outcomes after animal-derived surfactant therapy have consisted of small numbers of patients, with a variable proportion of survivors being tested. For both protein-free synthetic and animal-derived surfactant, the “long-term” outcomes reported consist of outcomes predominantly in the first 3 years of life, with very few reports of outcomes at school age or higher. Given these limitations, the evidence suggests that not only do more infants survive from surfactant therapy but they are also at no selective disadvantage for neurodevelopmental sequelae due to the surfactant therapy. Most comparisons of long-term outcomes have been between infants treated with surfactant and placebo. There are few or no comparisons of long-term outcomes between infants treated with different types of surfactant or different regimens of the same surfactant. The following sections mainly address comparisons between infants treated with surfactant and placebo.

28.1.3.5.1 Neurodevelopmental Outcomes

No significant differences have been reported in the long-term neurodevelopmental outcomes of infants treated with surfactant compared to those treated with placebo, either with protein-free synthetic surfactant (Corbet et al. 1995; Morley and Morley 1990; Courtney et al. 1995) or animal-derived surfactant (Hoekstra et al. 1994; Robertson et al. 1992; Dunn et al. 1988; Ferrara et al. 1991; Vaucher et al. 1988; Wagner et al. 1995; Ware et al. 1990).

28.1.3.5.2 Long-Term Respiratory Outcomes

Compared to infants treated with placebo, infants treated with surfactant in the neonatal period have been reported to have either improved (Abbasi et al. 1993; Pelkonen et al. 1998; Yuksel et al. 1993) or equivalent (Couser et al. 1993; Gappa et al. 1999; Walti et al. 1992) results on

pulmonary function testing. Some studies have reported a lower frequency of subsequent clinical respiratory disorders in surfactant-treated infants compared to placebo (Vaucher et al. 1988; Sell et al. 1995), while others have reported no difference (Robertson et al. 1992; Morley and Morley 1990; Dunn et al. 1988; Abbasi et al. 1993) or a trend towards an increase in allergic manifestations (Ware et al. 1990).

28.1.3.5.3 Physical Growth

No significant differences have been reported in weight or height outcomes between surfactant- and placebo-treated infants on follow-up (Corbet et al. 1995; Robertson et al. 1992; Courtney et al. 1995; Ware et al. 1990; Abbasi et al. 1993; Pelkonen et al. 1998; Gappa et al. 1999; Sell et al. 1995).

28.1.3.5.4 Outcomes of Prophylactic Versus Rescue Treatment Strategies

Two studies compared the long-term outcomes of infants treated with prophylactic surfactant to those treated with a “rescue” strategy. In one, there were no differences at school age in neurodevelopmental outcome or in the results of pulmonary function testing between the two groups, though infants who had received prophylactic surfactant showed fewer clinical pulmonary problems than those that received rescue treatment (Sinkin et al. 1998). In another study, in which there was significant loss of infants to follow-up (and therefore a high likelihood of attrition bias), the mean scores on the Bayley scales of infant development at 12 months adjusted age were higher in the rescue group than in the prophylactic group (Vaucher et al. 1993).

28.1.3.6 Exogenous Surfactant Therapy for Conditions Other than RDS

28.1.3.6.1 Meconium Aspiration Syndrome

In non-controlled studies of human infants with meconium aspiration syndrome, improved oxygenation has been reported with exogenous surfactant therapy (Auten et al. 1991; Halliday et al. 1996; Khammash et al. 1993). A randomized

trial in infants greater than 34 weeks gestation (including infants with MAS) with severe respiratory failure on extracorporeal membrane oxygenation (ECMO) showed that infants treated with beractant had improved lung function, a shorter duration of ECMO, and fewer complications after ECMO (Lotze et al. 1993).

Four randomized trials (Lotze et al. 1998; Findlay et al. 1996; Chinese Collaborative Study Group for Neonatal Respiratory Diseases 2005; Maturana et al. 2005) have studied the effect of animal-derived surfactant in term infants with meconium aspiration syndrome and are included in a systematic review. In these trials, surfactant therapy was administered as a continuous infusion over 20 min (Findlay et al. 1996) or as a bolus. The meta-analysis of these four trials (El Shahed et al. 2007) showed a decreased need for extracorporeal membrane oxygenation with surfactant therapy (typical RR 0.64, 95 % CI 0.46–0.91; typical ARD –0.17, 95 % CI –0.30 to –0.04). One trial reported a reduction in the length of hospital stay (mean difference –8 days (95 % CI –14 to –3 days)). There were no statistically significant effects on mortality (typical RR 0.98 (95 % CI 0.41–2.39), typical ARD 0.00 (95 % CI –0.05 to 0.05)) or other outcomes (duration of assisted ventilation, duration of supplemental oxygen, pneumothorax, pulmonary interstitial emphysema, air leaks, chronic lung disease, need for oxygen at discharge, or intraventricular hemorrhage).

In summary, infants with severe meconium aspiration syndrome are likely to benefit from treatment with animal-derived surfactants. Multiple doses are usually required in such infants. Only animal-derived surfactants have been tested in human clinical trials in this setting. Each dose should be administered cautiously, with close cardiac, respiratory, and oxygen saturation monitoring, because surfactant can aggravate preexisting airway obstruction from meconium and transient oxygen desaturation and endotracheal tube obstruction have been reported with bolus administration in nearly one-third of infants (Lotze et al. 1998).

Investigators have also attempted to treat MAS by lavaging the airways with diluted surfactant solutions in order to wash out residual meconium (Dargaville et al. 2007; Wiswell et al.

2002; Hung et al. 2006; Lista et al. 2006; Gadzinowski et al. 2008). When this approach was tested in a randomized trial with a small number of babies, there were no statistically significant differences in clinical outcomes, although there was a trend towards reduction in the combined outcome of death or need for ECMO (Dargaville et al. 2010).

28.1.3.6.2 Acute Respiratory Distress Syndrome

Surfactant dysfunction is well described in acute lung injury (Willson et al. 2008). Therefore, surfactant replacement has been proposed as a treatment for patients with acute lung injury and the acute respiratory distress syndrome (ARDS), which, although more common in adults and older children, can occur in term neonates (Faix et al. 1989; Pfenninger et al. 1991). Exogenous surfactant therapy has been attempted in ARDS in adults but the results of clinical trials have not been promising (Anzueto et al. 1996; Gregory et al. 1997a). There are no randomized trials of exogenous surfactant therapy specifically for ARDS in neonates, but in older children with acute respiratory failure, surfactant use decreased mortality and duration of ventilation (Willson et al. 1999; Duffett et al. 2007). Because of this, and based on the pathophysiologic, clinical, and radiologic similarities between RDS and ARDS, it is reasonable to provide exogenous surfactant therapy to term infants with clinical and radiologic features of ARDS (severe respiratory failure with pulmonary opacification and air bronchograms on chest radiographs). The use of surfactant in ARDS is discussed in detail in Sect. 28.2.

28.1.3.6.3 Other Conditions

There are reports (single-case reports or case series) of the use of exogenous surfactant therapy in human infants for the management of pulmonary hemorrhage (Pandit et al. 1995; Amizuka et al. 2003) and neonatal pneumonia (Auten et al. 1991; Robertson 1996; Herting et al. 2000; Fetter et al. 1995). However, the efficacy of surfactant in these conditions is uncertain and its routine use in these conditions cannot be recommended. Surfactant therapy for infants with congenital diaphragmatic hernia has also been attempted

(Bos et al. 1991; Lotze et al. 1994; Glick et al. 1992; Lally et al. 2004; Van Meurs and Congenital Diaphragmatic Hernia Study Group 2004) but actually resulted in worse outcomes and therefore is not recommended.

28.1.4 Future Developments

Future research in neonatal surfactant therapy will likely attempt to understand the functioning and clinical effects of protein-containing synthetic surfactants. Emerging research is also addressing different methods of surfactant delivery to the lungs.

Surfactant administration through a laryngeal mask airway is noninvasive, avoids endotracheal intubation, and has been reported in a series of eight preterm infants with RDS managed with nasal CPAP (Trevisanuto et al. 2005). The mean arterial-to-alveolar oxygen tension ratio improved significantly after the treatment and no complications were reported. This method of administration is promising, as it potentially avoids the complications associated with intubation, but requires testing in a large randomized trial before it can be recommended.

Another noninvasive method of surfactant administration is instillation of surfactant into the nasopharynx during or immediately after delivery and before the first breath. Such instillation is thought to cause the surfactant to be aspirated into the fluid-filled airway as an air–fluid interface is established. A case series (Kattwinkel et al. 2004) of 23 preterm infants 27–30 weeks receiving such intrapartum nasopharyngeal instillation of surfactant followed by placement on CPAP immediately after birth (mask CPAP initially followed by nasal CPAP) demonstrated the feasibility of such administration. However, more evidence is required to prove the efficacy of this approach before it can be used or recommended.

The administration of surfactant to spontaneously breathing infants on nasal CPAP by passing a thin catheter into the trachea has been reported, initially from a single center (Kribs et al. 2008) and subsequently from a nonrandomized multicenter study (Kribs et al. 2010). While this method is promising, it requires rigorous evaluation in randomized trials. It is now being

evaluated in a multicenter study called the AMV (Avoid Mechanical Ventilation) trial.

Finally, future research is likely to (or should) address methods of better identifying infants with respiratory disorders who would benefit from surfactant therapy. Current methods of selecting infants for surfactant therapy are primarily demographic (e.g., infants below a certain gestation), clinical (signs of respiratory distress with oxygen requirement), or radiographic (radiographic features of RDS). The development of more sophisticated and highly accurate tests to identify infants who will benefit from surfactant and those in whom surfactant therapy is not required will be very useful to clinicians.

Essentials to Remember

- Exogenous surfactant therapy is now a standard therapy for respiratory distress syndrome. Numerous randomized controlled trials have proved its efficacy and compared different products and treatment strategies.
- In infants with RDS, surfactant should be administered as early as possible after its need is identified.
- Animal-derived surfactant products are superior to protein-free synthetic surfactants. A new class of protein-containing synthetic surfactants is being tested for efficacy and might prove to have an important role in exogenous surfactant therapy in the future.
- While prophylactic surfactant administration to preterm infants at risk of RDS was previously the preferred practice compared to “rescue” surfactant administration, emerging new evidence suggests that initial stabilization of preterm infants on nasal continuous positive airway pressure might be equally effective, requires fewer resources, and avoids ventilator-induced lung injury.
- Exogenous surfactant therapy has potential benefits in term infants with meconium aspiration syndrome.

28.2 Exogenous Surfactant in the Pediatric Patient

Douglas Willson

Educational Aims

- To briefly review the history of surfactant therapy in neonates and in older children and adults
- To review the physiology underlying the potential value of exogenous surfactant therapy in ALI/ARDS
- To describe the different types of pharmaceutical surfactants
- To detail the animal and human studies examining the effects of exogenous surfactant in ALI/ARDS
- To speculate on the future role of exogenous surfactant as a component of therapy for ALI/ARDS

28.2.1 Introduction

With the identification of surfactant deficiency as the putative cause of infantile respiratory distress syndrome (IRDS) by Avery and Mead in 1959 (Avery and Mead 1959) and the closely following recognition of dipalmitoyl phosphatidylcholine (DPPC) as a major surfactant lipid component (Brown 1962, 1964), it was not long before treatment with this compound as a substitute “lung surfactant” was attempted. The studies of both Robillard et al. in 1964 (1964) and Chu et al. in 1967 (1967) tried unsuccessfully to treat infants with established IRDS (called hyaline membrane disease at the time) using aerosolized DPPC. The failure of this initial “surfactant replacement therapy,” together with a small but apparently positive physiological response to pulmonary vasodilatation, led to the erroneous conclusion that IRDS was due to ischemia and that surfactant deficiency was the result and not the cause of this disease (Chu et al. 1965, 1967). This misinterpretation was widely accepted until Enhorning and colleagues (Enhorning et al. 1973a, b) in

1973 demonstrated that whole surfactant isolated from adult rabbits could induce near-normal gas exchange when instilled into the trachea of premature rabbit pups, documenting that their respiratory failure was caused by surfactant deficiency. Moreover, it was not until 1981 that Fujiwara et al. (Fujiwara 1981) reported positive responses in respiratory function in human infants treated with a bovine-derived exogenous lung surfactant. We now understand that pulmonary surfactant is more than just DPPC, and that multiple lipid and peptide components are required for full activity. It is also now appreciated that the attempts of Robillard et al. (1964) and Chu et al. (1967) to aerosolize DPPC were not effective in delivering adequate amounts of material to the alveoli. Intratracheal instillation of exogenous surfactants in aqueous suspension is the current standard of care for the treatment and prevention of IRDS.

The ongoing development of surfactant therapy for clinical acute lung injury (ALI) and the acute (formerly “adult”) respiratory distress syndrome (ARDS) has been subject to some of the same issues that occurred during early attempts at this intervention in premature infants with IRDS. It has been known for some time that endogenous surfactant becomes dysfunctional in many forms of acute inflammatory lung injury, providing a direct conceptual rationale for exogenous surfactant supplementation. Despite this rationale, initial controlled studies attempting to treat adults with ARDS with exogenous surfactants were unsuccessful (Anzueto et al. 1996; Gregory et al. 1997b) and prompted calls for abandoning further clinical trials (Matthay 1996). However, the exogenous surfactants used in these studies (Anzueto et al. 1996; Gregory et al. 1997b) lacked one or more highly active components found in native surfactant, and the patients had sepsis-induced ARDS that involved substantial extrapulmonary pathology. Other studies of exogenous surfactant therapy in patients with ALI/ARDS give reason for cautious optimism about the use of this intervention, particularly in the case of direct pulmonary forms of these syndromes. This chapter briefly reviews the history and rationale for surfactant therapy in ALI/ARDS.

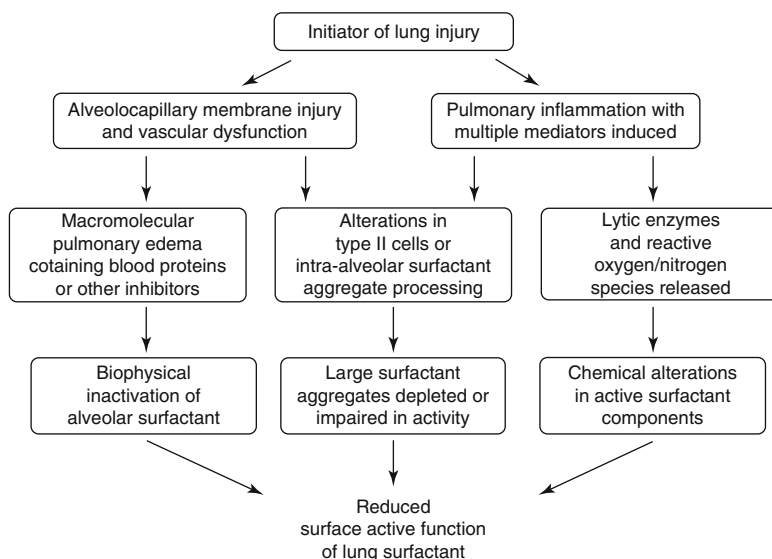


Fig. 28.5 Schematic diagram illustrating pathways that can contribute to surfactant dysfunction in acute inflammatory pulmonary injury. Initiators of lung injury can act initially either from the alveolar side (“direct” lung injury) or from the vascular side (“indirect” or “extrapulmonary” lung injury). However, both direct and indirect etiologies of injury induce pulmonary inflammation, alveolocapillary membrane injury, permeability edema, and reactive

vasoconstriction or related vascular dysfunction. Surfactant dysfunction can occur by multiple mechanisms in the injured lungs, as shown in the figure and described in the text. The resulting loss of surface-active function contributes to acute respiratory failure with decreased lung volumes, decreased compliance, and severe ventilation/perfusion mismatching (Adapted from Wang et al. (2005a))

28.2.2 Evidence of Surfactant Dysfunction in ALI/ARDS

Unlike IRDS, surfactant deficiency is not a major factor in most forms of ALI/ARDS. Instead, surfactant dysfunction (inactivation, inhibition) induced by inflammatory lung injury is an important contributor to pathophysiology. In ALI/ARDS, an initially functional pulmonary surfactant system becomes “collateral damage” during whatever primary process injures the lung. Surfactant dysfunction can occur whether the cause of lung injury originates on the alveolar side of the epithelium (so-called direct lung injury such as from aspiration, pulmonary bacterial or viral infection, pulmonary oxygen toxicity) or from the vascular side (“indirect” or “extrapulmonary” lung injury, such as in association with sepsis, shock, fatty acid release from long bone fracture or pancreatitis, burn injury, multiple blood transfusions). During both direct and indirect lung injury, initially active surfactant can be rendered dysfunctional by one of several

mechanisms (Fig. 28.5) (Jobe and Ikegami 1998b; Notter and Wang 1997; Wang et al. 2005a; Notter 2000):

1. Inhibition of surfactant biophysical function by plasma proteins (Holm et al. 1985; Seeger et al. 1985a, b, 1993; Holm and Notter 1987; Holm et al. 1988; Fuchimukai et al. 1987; Keough et al. 1989; Wang and Notter 1998;) or other blood components such as fatty acids (Wang and Notter 1998; Seeger et al. 1985b; Hall et al. 1990, 1992b, 1994; Holm et al. 1999) that leak into the alveolar space as a result of alveolocapillary membrane injury and decreased barrier integrity
2. Alterations in alveolar surfactant aggregates whereby the most active “large aggregate” forms of surfactant are reduced in activity and/or percent content, while less active “small aggregate” forms of surfactant become more prevalent (Wang et al. 2005a; Hall et al. 1994; Davidson et al. 2005; Russo et al. 2002, 2007; Wright et al. 2001; Hickman-Davis et al. 2007; Raghavendran et al. 2008a; Lewis

- et al. 1990; Günther et al. 1996; Veldhuizen et al. 1995)
3. Inhibition and/or chemical alteration of components in the alveolar surfactant film induced by cell membrane lipids (Holm and Notter 1987; Wang and Notter 1998; Holm et al. 1999; Cockshutt and Possmayer 1991; Wang et al. 2005b, 2008), meconium (Moses et al. 1991), or other substances present during the innate pulmonary inflammatory response such as proteases (Pison et al. 1989a), phospholipases (Holm et al. 1991; Enhorning et al. 1992; Wang et al. 2007), or reactive oxygen/nitrogen species (Seeger et al. 1985b; Hickman-Davis et al. 2001; Haddad et al. 1993; Amirkhanian and Merritt 1998)
 4. An altered synthesis, secretion, or composition of active surfactant due to injury-induced changes in alveolar type II pneumocytes, which are stem cells for the alveolar epithelium in addition to being the primary cells of lung surfactant metabolism (Finkelstein 1990; Finkelstein et al. 1992; Mason et al. 1977; Mason and Williams 1997)

Abnormalities in surfactant composition and/or activity have been well documented in bronchoalveolar lavage (BAL) from patients with many forms of ALI/ARDS e.g., (Günther et al. 1996; Veldhuizen et al. 1995; Seeger et al. 1990; Pison et al. 1989b; Gregory et al. 1991; Griese 1999; Schmidt et al. 2007; Greene et al. 1999). Regardless of etiology, the practical consequences of surfactant dysfunction in ALI/ARDS are not dissimilar to those found in IRDS. As a result of decreased surfactant activity, the lungs become less compliant, with a progressive loss of aerated volume and an increased mismatching of ventilation with perfusion. Hypoxia, respiratory failure, and the need for respiratory support then ensue. In addition to surfactant dysfunction, ALI/ARDS also involves pulmonary inflammation and vascular dysfunction that can significantly impact overall patient outcomes and responses to therapy. Moreover, systemic inflammation and multiorgan (extrapulmonary) pathology are prominent in “indirect” forms of ALI/ARDS. The complex pathophysiology of ALI/ARDS is reviewed elsewhere (e.g., Bernard et al. 1994;

Ware and Matthay 2000; Knight and Rotta 2005; Artigas et al. 1998; Krafft et al. 1996; Rubenfeld et al. 2005; Raghavendran et al. 2008b; DeBruin et al. 1992; Flori et al. 2005).

In considering surfactant dysfunction and therapy in ALI/ARDS, it is also important to have the perspective that lung injury is not a static phenomenon. Surfactant dysfunction, and hence surfactant replacement, is most important mechanistically in the acute exudative phase of ALI/ARDS. However, lung injury can progress to more chronic fibroproliferative and fibrotic stages, including superimposed effects from iatrogenic barotrauma, volutrauma, or atelectrauma induced by mechanical ventilation (“ventilator induced lung injury,” VILI) (Dos Santos and Slutsky 2000; Ricard et al. 2001; The Acute Respiratory Distress Syndrome Network 2000; Pelosi and Negrini 2008). The presence of evolving lung injury, together with inflammation and other non-surfactant factors in the pathophysiology of ALI/ARDS, complicates assessments of the long-term efficacy of exogenous surfactant therapy. Even if acute surfactant dysfunction is reversed effectively, long-term therapeutic benefits may not be apparent due to the presence of other aspects of disease. The long-term efficacy of surfactant therapy also depends on the specific activity of the exogenous surfactant used, the method of surfactant delivery, and almost certainly other variables that remain to be elucidated.

28.2.3 In Vitro Studies of Surfactant Inhibition

As noted above, multiple biophysical studies in vitro have shown that surfactant activity is reduced by exposure to albumin, hemoglobin, lysophospholipids, fatty acids, and other chemicals associated with lung injury ((Notter and Wang 1997; Wang et al. 2005a; Notter 2000) for detailed review). Importantly, these studies also document that inhibitor-induced inactivation can be overcome by raising surfactant concentration. The ability of exogenous surfactant supplementation to overcome inhibition in vitro is

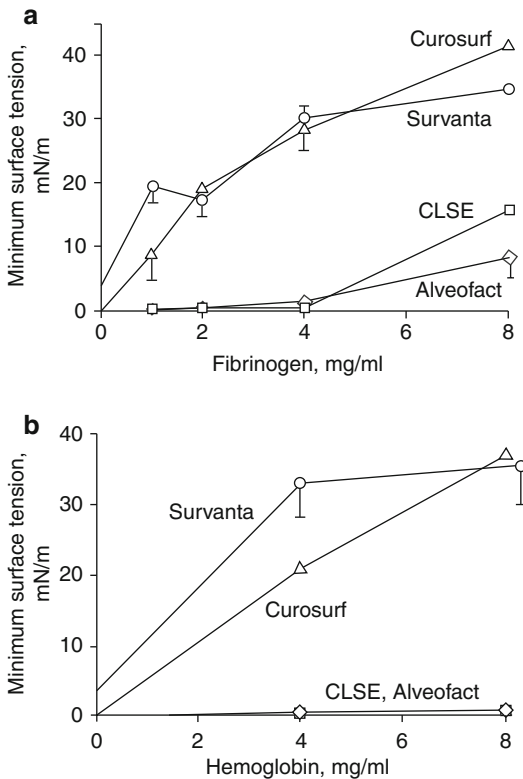


Fig. 28.6 Resistance of different clinical surfactants to inhibition by blood proteins. The graph shows the minimum surface tension reached by different clinical surfactants after 5 min of pulsation in a bubble surfactometer (37 °C, 20 cycles/min, 50 % area compression) in the presence of different concentrations of inhibitory blood proteins (fibrinogen (a) and hemoglobin (b)). Exogenous surfactants that most closely mimic natural surfactant (CLSE/Infasurf® and Alveofact®) are best able to resist inhibition and reach low surface tensions despite high levels of inhibitory proteins. Clinical exogenous surfactants are described and categorized in more detail in a subsequent section. Surfactant concentration for all preparations shown was uniform at 2 mg/ml (Data are from Seeger et al. (1993) as adapted by Notter (2000))

not only a function of surfactant concentration but also depends on the content of essential apoproteins, particularly surfactant protein (SP)-B. Exogenous surfactants with higher contents of SP-B generally have greater activity and better inhibition resistance than those with little or no SP-B (Fig. 28.6). This is particularly relevant clinically, because the two major surfactant drugs studied unsuccessfully in the 1990s in controlled trials in adults with ARDS contained

either no SP-B (Exosurf®) (Anzueto et al. 1996) or minimal levels of SP-B (Survanta®) (Gregory et al. 1997b).

28.2.4 Animal Studies of Exogenous Surfactant Therapy In Vivo

The effects of exogenous surfactant replacement have been studied in a large number of animal models of acute pulmonary injury (ALI/ARDS). Animal studies of acute injury most commonly examine responses to therapy over a timescale of hours, although some (e.g., hyperoxia) can address effects over longer times. Animal studies of acute pulmonary injury offer limited insight into long-term efficacy and the mitigation of chronic pathology, but are essential in providing a direct measure of the effectiveness of exogenous surfactants in mitigating injury-induced surfactant dysfunction and associated acute respiratory failure. Data from animal experiments on surfactant therapy have given insights into optimal preparations and delivery methods and are reassuring with regard to safety. Selected findings relating to exogenous surfactants and their efficacy in animal models of lung injury include the following (see Refs (Wang et al. 2005a; Notter 2000) for further review of animal studies of surfactant therapy in ALI/ARDS):

Type of lung injury: “Direct” lung injuries in animal models such as saline lavage (Lachmann et al. 1983; Kobayashi et al. 1984; Berggren et al. 1986; Lewis et al. 1996; Walther et al. 1997, 1998), acid aspiration (Kobayashi et al. 1990; Zucker et al. 1992; Schlag and Strohmaier 1993), viral infection (van Daal et al. 1991, 1992), or hyperoxic injury (Matalon et al. 1987, 1988; Loewen et al. 1989; Engstrom et al. 1989; Novotny et al. 1995) have been shown to respond well to the instillation of active exogenous surfactants. In contrast, significant benefits from surfactant replacement have not been documented in animal models of “indirect” lung injuries from systemic sepsis or intravenous oleic acid administration.

Type of surfactant: Surfactant preparations containing high levels of the hydrophobic surfactant proteins SP-B and SP-C are more effective physiologically than protein-free synthetic surfactants. Additionally, SP-B is known to have greater efficacy than SP-C in enhancing biophysical and physiological activity in exogenous surfactant mixtures (Curstedt et al. 1987; Oosterlaken-Dijksterhuis et al. 1991a, b, 1992; Revak et al. 1988; Seeger et al. 1992; Wang et al. 1996, 2002; Yu and Possmayer 1988; Notter et al. 2002), and supplementation with purified SP-B or synthetic SP-B peptides increases the activity of surfactants that contain SP-C in animal models of surfactant replacement (Walther et al. 1997; Notter et al. 2002; Mizuno et al. 1995).

Timing of administration: Early as opposed to late administration of exogenous surfactant has the most potential efficacy in ALI/ARDS for several reasons: (a) a better distribution of exogenous surfactant is possible because lung injury is more homogeneous early on; (b) early surfactant administration can help to moderate subsequent ventilator-induced lung injury; and (c) surfactant deficiency/dysfunction is most pronounced, and can be most specifically targeted, early in the course of lung injury. The benefits of early exogenous surfactant therapy have previously been documented clinically in premature infants (Bevilacqua et al. 1996; Kattwinkel et al. 1993; Kendig et al. 1998, 1991; OSIRIS Collaborative Group 1992).

Method of delivery: Delivery of exogenous surfactants by direct airway instillation has been found to be more effective than aerosolization (Notter 2000; Lewis et al. 1991, 1993a, b). Despite the theoretical advantages of aerosolization, it has proven difficult to deliver adequate amounts of surfactant to the alveoli using current technology. Also, aerosolized surfactant tends to go where inspired gas goes and consequently may not reach and recruit poorly aerated lung regions effectively (Lewis et al. 1993a, b).

Other variables: The efficacy of exogenous surfactants can also be affected by the method

Table 28.2 Approximate biochemical composition of endogenous pulmonary surfactant

85–90 % phospholipids
80 % phosphatidylcholine (PC)
40–50 % DPPC
10–15 % other disaturated PCs
35–45 % unsaturated PCs
15 % anionic phospholipids (PG, PI, PS)
5 % other phospholipid classes (PE, Sph)
7–10 % apoproteins
SP-A
SP-B
SP-C
SP-D (not involved in biophysical function)
4–7 % neutral lipids
Cholesterol
Cholesterol esters
Glycerides

Adapted from the research text of Notter (2000)

Values are representative averages in weight percent for surfactant lavaged (washed) from the lungs of normal animals of different species and ages

Abbreviations: PC phosphatidylcholine, PG phosphatidylglycerol, PI phosphatidylinositol, PS phosphatidylserine, PE phosphatidylethanolamine, Sph sphingomyelin, SP surfactant protein

or mode of mechanical ventilation (Van Kaam et al. 2004), dosage amount and concentration, surfactant viscosity (King et al. 2002), rate of delivery, and other physical variables. Further animal studies, however, are necessary in order to study these variables systematically.

Ultimately, although animal studies have been (and are) indispensable in assessing exogenous surfactants and their physiological effects and activity, therapeutic efficacy must be determined in clinical studies where important outcome variables are directly assessed in patients.

28.2.5 Pharmaceutical Surfactants

Pharmaceutical surfactants and native pulmonary surfactant are not identical. Endogenous lung surfactant is a complex mixture of lipids (primarily phospholipids) and specific apoproteins that is highly conserved across mammalian species (Table 28.2). The degree of resemblance of native

surfactant to pharmaceutical surfactants is highly variable, and the latter can be divided into three functionally relevant groups (Notter 2000; Notter and Wang 2008; Chess et al. 2005):

- I. Organic solvent extracts of lavaged lung surfactant from animals (*Alveofact*[®], *BLES*[®]; *Infasurf*[®])
- II. Organic solvent extracts of processed animal lung tissue with or without additional synthetic additives (*Curosurf*[®]; *Survanta*[®] or *Surfactant-TA*[®])
- III. Synthetic preparations not containing surfactant material from animal lungs (*ALEC*; *Exosurf*[®]; *Surfaxin*[®]; *Venticute*[®])

Surfactants in Categories I and II are sometimes classified together as “animal-derived” or “natural” surfactant preparations. However, clinical surfactants in Category I have the closest compositional analogy to endogenous surfactant because they are obtained directly from recovered alveolar lavage fluid. Category I surfactant preparations in principle contain all the surfactant phospholipids plus the two hydrophobic surfactant proteins SP-B and SP-C in close approximation to the natural ratio (the hydrophilic surfactant proteins SP-A and SP-D are removed by organic solvent extraction in all Category I and Category II surfactants). Surfactant preparations in Category II also contain surfactant phospholipids and one or both of the hydrophobic surfactant proteins, but in addition they potentially contain constituents such as cellular lipids and/or hydrophobic fragments of cellular proteins because they are derived from processed lung tissue.

In addition to animal-derived surfactants, there is significant current interest in developing improved synthetic surfactant drugs (Category III surfactants above). Two early protein-free synthetic surfactants (*ALEC* and *Exosurf*[®]) are now no longer used because their activity is significantly less than existing animal-derived surfactants. Two newer synthetic surfactants are *Surfaxin*[®] (KL4) and *Venticute*[®] (recombinant SP-C surfactant). However, the 21 amino acid KL4 peptide in *Surfaxin*[®] has only very approximate molecular analogy to native SP-B, and *Venticute*[®] contains no SP-B peptide. Thus, the

development of more optimal fully synthetic surfactants with a highly active SP-B peptide component with or without added novel lipids that can resist phospholipase-induced degradation in lung injury is an active area of investigation (Notter 2000; Wang et al. 2003, 2007; Notter and Wang 2008; Notter et al. 2007). Synthetic lung surfactants have significant potential advantages in purity, manufacturing, quality control, scale-up, and cost relative to animal-derived preparations (Notter and Wang 2008; Notter et al. 2007). Synthetic surfactants are also free from animal pathogens like prions, and they are not subject to cultural or religious issues that can affect bovine- or porcine-derived preparations. Simple dosage calculations illustrate the potential practical importance of synthetic surfactants in ALI/ARDS, since drug amounts 50–100 times larger than those used in premature infants are required in adults and older children to achieve an equivalent dose normalized by body weight. The dollar expense of surfactant therapy in adult patients will be extremely high unless drug costs per unit weight can be reduced substantially from the current price of 100–200 mg infant vials of animal-derived surfactants. Synthetic surfactant production involves no animal costs, and chemical manufacturing methods can theoretically be scaled-up and quality controlled much more efficiently to allow more cost-effective therapy of ALI/ARDS.

Regardless of category (animal-derived or synthetic), the requirements for an effective therapeutic surfactant in ALI/ARDS are more stringent than in the case of IRDS. To treat severe acute inflammatory lung injury, exogenous surfactants must have the greatest possible activity and resistance to inhibition or inactivation. Specific differences in composition among clinical exogenous lung surfactants are a major factor in predicting and interpreting their clinical efficacy. For example, the protein-free exogenous surfactant *Exosurf*[®] has some activity in treating IRDS (Bose et al. 1990; Corbet et al. 1991; Long et al. 1991a, b), but it is significantly less efficacious in premature infants than apoprotein-containing animal surfactants like *Infasurf*[®] (Hudak et al. 1996, 1997; Notter 2000), and it has

no clinical benefits in adults with ARDS (Anzueto et al. 1996). Similarly, Survanta® has been found to have minimal benefits in adults with sepsis-induced ARDS (Gregory et al. 1997b), which correlates with its very low content of active SP-B (Seeger et al. 1993; Mizuno et al. 1995; Hamvas et al. 1994). At the same time, Survanta® has significant activity due to its content of SP-C (Notter et al. 2002), and it is efficacious in treating premature infants with IRDS as well as term infants with acute respiratory failure from meconium aspiration lung injury as detailed later (Khammash et al. 1993; Lotze et al. 1993, 1998; Findlay et al. 1996).

SP-B, the larger and most biophysically active (Curstedt et al. 1987; Oosterlaken-Dijksterhuis et al. 1991a, b, 1992; Revak et al. 1988; Seeger et al. 1992; Wang et al. 1996, 2002; Yu and Possmayer 1988; Notter et al. 2002) of the two hydrophobic surfactant proteins, is a particularly essential component for optimal surfactant function in vivo. Knock-out mice with isolated SP-B deficiency die shortly after birth of respiratory failure (Clark et al. 1995), and human infants with SP-B mutations do not survive beyond the first days of life without surfactant replacement (and ultimately lung transplant) (Hamvas et al. 1994, 1995, 1997; Whitsett et al. 1995). An elegant series of experiments by Ikegami et al. (2005) using a conditional knock-out mouse model demonstrated that adult mice rendered acutely deficient in SP-B develop severe respiratory distress with evidence of surfactant dysfunction and pulmonary inflammation. Mice left SP-B deficient died with pathology resembling ARDS, but the abnormalities were reversed and the mice survived if SP-B synthesis was restored. Interestingly, these mice maintained normal levels of the SP-C protein during study (Ikegami et al. 2005).

28.2.6 Human Studies of Surfactant Therapy for ALI/ARDS

Multiple clinical studies have reported measurable benefits following the instillation of active exogenous surfactants to term newborns,

children, or adults with ALI/ARDS or lung injury-related acute respiratory failure (Auten et al. 1991; Khammash et al. 1993; Lotze et al. 1993, 1998; Findlay et al. 1996; Willson et al. 1996, 1999, 2005; Gunther et al. 2002; Walmrath et al. 1996, 2002; Spragg et al. 1994; Wiswell et al. 1999; Lopez-Herce et al. 1999; Hermon et al. 2002; Herting et al. 2002; Luchetti et al. 1998, 2002; Moller et al. 2003; Amital et al. 2008) (Table 28.3). However, while a number of these have been controlled trials, many have been uncontrolled pilot studies or case series that reported significant improvements primarily in acute lung function (arterial oxygenation). Moreover, as noted earlier, two large controlled trials not included in the positive studies in Table 28.3 either showed no benefit (Anzueto et al. 1996) or minimal benefits (Gregory et al. 1997b) from surfactant therapy in adults with sepsis-induced ARDS. A more detailed summary of the clinical experience with surfactant therapy in term infants, children and adults with ALI/ARDS follows below.

Perhaps the best-studied application of surfactant therapy for an indication other than IRDS is in full-term infants with meconium aspiration syndrome (MAS) (Auten et al. 1991; Khammash et al. 1993; Lotze et al. 1993, 1998; Findlay et al. 1996). Meconium is a thick, tarry mixture of bile acids and mucous glycoproteins that fills the fetal colon during gestation, and prenatal defecation associated with maternal/fetal stress can lead to meconium aspiration at birth. Meconium mechanically obstructs airways, causes inflammation (Holopainen et al. 1999), and inhibits the biophysical activity of lung surfactant (Moses et al. 1991; Clark et al. 1987). Auten et al. (1991), Khammash et al. (1993), and Findlay et al. (1996) have all reported significant lung functional improvements following exogenous surfactant administration (Infasurf®, Survanta®) to infants with MAS. The randomized study of Findlay et al. (1996) also found significant reductions in the incidence of pneumothorax, duration of mechanical ventilation and oxygen therapy, time of hospitalization, and requirements for ECMO in 20 term infants with MAS treated with Survanta® compared to a similar number of

Table 28.3 Selected controlled and uncontrolled clinical studies reporting benefits of exogenous surfactant therapy in acute respiratory failure (ALI/ARDS)

Study	Patients (N)	Disease	Surfactant	Outcomes
Günther et al. (2002).	Adults (27)	ARDS	Alveofact®	Improved surfactant function
Walmrath et al. (2002)	Adults (10)	ARDS, sepsis	Alveofact®	Improved oxygenation
Spragg et al. (1994)	Adults (6)	ARDS, multiple causes	Curosurf®	Improved oxygenation and biophysical function
Wiswell et al. (1999)	Adults (12)	ARDS, multiple causes	Surfaxin®	Improved oxygenation
Amital et al. (2008).	Adults (42)	Lung transplant	Infasurf®	Improved oxygenation, better graft function
Willson et al. (1996, 1999)	Children (29 & 42)	ARDS, multiple causes	Infasurf®	Improved oxygenation
Willson et al. (2005)	Children (152)	ARDS, multiple causes	Infasurf®	Improved survival and improved ventilation
Lopez-Herce et al. (1999)	Children (20)	ARDS + post-op cardiac	Curosurf®	Improved oxygenation
Hermon et al. (2002)	Children (19)	ARDS + post-op cardiac	Curosurf® or Alveofact®	Improved oxygenation
Herting et al. (2002)	Children (8)	Pneumonia	Curosurf®	Improved oxygenation
Moller et al. (2003)	Children (35)	ARDS, multiple causes	Alveofact	Improved oxygenation
Auten et al. (1991)	Infants (14)	MAS or pneumonia	Infasurf® (CLSE)	Improved oxygenation
Lotze et al. (1993, 1998)	Infants (28 & 328)	ECMO, multiple indications	Survanta®	Improved oxygenation, decreased ECMO
Khammash et al. (1993)	Infants (20)	MAS	bLES®	Improved oxygenation in 75 % of patients
Findlay et al. (1996)	Infants (40)	MAS	Survanta®	Improved oxygenation, decreased pneumothorax, and mechanical ventilation
Luchetti et al. (1998; 2002)	Infants (20 & 40)	RSV bronchiolitis	Curosurf®	Improved oxygenation

The tabulated studies of Willson et al. (1999; 2005), Findlay et al. (1996), Moller et al. (2003), Lotze et al. (1993, 1998), Luchetti et al. (1998, 2002), and Amital et al. (2008) were controlled trials, while the remaining studies were uncontrolled pilot trials as detailed in the text

MAS meconium aspiration syndrome, RSV respiratory syncytial virus

controls. Lotze et al. (1993, 1998) have also reported favorable results using Survanta® in a controlled trial in term infants referred for ECMO due to severe respiratory failure (meconium aspiration was a prevalent diagnosis). Twenty-eight infants treated with four doses of Survanta® (150 mg/kg) had improved pulmonary mechanics, decreased duration of ECMO treatment, and a lower overall incidence of complications after ECMO compared to control infants (Lotze et al. 1993). A subsequent larger multicenter controlled trial in 328 term infants similarly reported significant improvements in respiratory status

and the need for ECMO following surfactant treatment (Lotze et al. 1998). Exogenous surfactant is now used in many institutions to treat neonates with MAS. Surfactant therapy is also frequently used in intensive care nurseries to treat neonates with respiratory failure from pneumonia, although controlled studies in the NICU setting have not been done.

Experience with clinical surfactant therapy in adults with ALI/ARDS is much less positive than in infants. Several small uncontrolled studies in adults with ALI/ARDS have reported acute lung functional improvements following surfactant

treatment (Gunther et al. 2002; Walmrath et al. 1996, 2002; Spragg et al. 1994; Wiswell et al. 1999) (Table 28.3). In contrast, the influential large controlled trial of Anzueto et al. (1996) administered nebulized Exosurf® *versus* placebo in 725 adults with ARDS secondary to sepsis and found no improvement in any measure of oxygenation and no effect on morbidity or mortality. As noted earlier, this study is now recognized as having several flaws: (1) the synthetic protein-free surfactant Exosurf® has significantly lower activity than animal-derived surfactants; (2) current aerosol technology has not been found to be as effective as airway instillation in administering surfactant (the surfactant dose delivered was estimated to be 5 mg/kg/day as opposed to the standard 100 mg/kg instilled dose used in infants with IRDS); and (3) recent data indicate that surfactant is less effective in treating ALI/ARDS from sepsis or other “indirect” causes of lung injury compared to “direct” pulmonary ALI/ARDS.

Two other controlled clinical trials reporting disappointing results in adults with ALI/ARDS are those of Gregory et al. (1997b) with Survanta® and Spragg et al. (2003) with recombinant SP-C surfactant (Venticute®). These results reinforce the importance of including highly active SP-B in exogenous surfactants used to treat ALI/ARDS in adults, since Survanta® contains only minimal levels of this apoprotein (Seeger et al. 1993; Mizuno et al. 1995; Hamvas et al. 1994) and Venticute® contains none. The trial of Gregory et al. (1997b) found small benefits in oxygenation for patients with sepsis-induced ALI/ARDS who received intermediate-sized doses of Survanta® (100 mg/kg), but no benefits in other surfactant dosage groups. There were no overall long-term benefits from surfactant therapy as measured by length of mechanical ventilation or survival in the total of 43 surfactant-treated patients studied (Gregory et al. 1997b). The study of Spragg et al. (2003) showed acute increases in oxygenation following instillation of Venticute® in adults with ARDS, but no longer-term improvements (duration of mechanical ventilation, length of stay, or mortality). A post hoc analysis suggested possible benefits from surfactant therapy in the subgroup of patients with

ARDS from “direct” lung injury. However, a follow-up randomized trial of Venticute® limited to patients with direct lung injury was recently stopped after 900 patients because of a failure to demonstrate clinical benefits (Spragg R, 2009, personal communication).

Controlled studies of surfactant therapy in children with ALI/ARDS have been much more encouraging compared to studies in adults. Luchetti et al. (1998, 2002) have reported two small controlled studies showing that treatment with porcine surfactant (Curosurf®, 50 mg/kg) improved gas exchange plus led to a reduced time on mechanical ventilation and in the pediatric intensive care unit (PICU) for infants with RSV bronchiolitis. An eight center randomized unblinded trial by Willson et al. (1999) in 42 children in the PICU with ALI/ARDS showed that those receiving Infasurf® (70 mg/kg) had immediate improvements in oxygenation and fewer ventilator days and days in intensive care. This trial followed an initial uncontrolled treatment study by the same group indicating improved oxygenation in 24 children (0.1–16 years) with ALI/ARDS treated with instilled Infasurf® (Willson et al. 1996). A study by Moller et al. (2003) has also reported that children with ARDS showed immediate improvement in oxygenation and less need for rescue therapy following treatment with Survanta®, but was underpowered to assess more definitive longer-term outcomes.

A larger and more recent blinded controlled study in 2005 by Willson et al. (2005) in PICU patients with ALI/ARDS showed that treatment with Infasurf® (calfactant) relative to placebo was associated both with immediate benefits to oxygenation as well as a significant survival advantage (Table 28.4). In a post hoc analysis, all of the benefits of surfactant therapy were in the 98-patient subgroup with “direct” pulmonary forms of ALI/ARDS (Table 28.5). The 54-patient subgroup with “indirect” forms of ALI/ARDS showed no acute or long-term benefits from calfactant. The significant benefits of calfactant in treating direct pulmonary ALI/ARDS in children found by Willson et al. (2005) have prompted an even larger prospective trial in both adults and children with direct lung injury (CARDS, Calfactant in ARDS trial, NCT00682500).

Table 28.4 Clinical outcomes from the randomized controlled trial of exogenous surfactant (calfactant) therapy in pediatric acute lung injury of Willson et al. (2005)

	Calfactant (n=77)	Placebo (n=75)	P value
<i>Mortality</i>			
Died (in hospital)	15 (19 %)	27 (36 %)	0.03
Died w/o extubation	12 (16 %)	24 (32 %)	0.02
Failed CMV ^a	13 (21 %)	26 (42 %)	0.02
ECMO	3	3	n.s.
Use of nitric oxide	9	10	0.80
HFOV after entry	7	15	0.07
<i>Secondary outcomes^b</i>			
PICU LOS	15.2±13.3	13.6±11.6	0.85
Hospital LOS	26.8±26	25.3±32.2	0.91
Days of O ₂ therapy	17.3±16	18.5±31	0.93
Hospital charges ^c	\$205±220	\$213±226	0.83
Hospital charges/day ^c	\$ 7.5±7.6	\$ 7.9±7.5	0.74

Data from Willson et al. (2005)

Calfactant Infasurf®, *CMV* conventional mechanical ventilation, *ECMO* extracorporeal membrane oxygenation, *HFOV* high-frequency oscillatory ventilation, *NO* nitric oxide therapy, *PICU* pediatric intensive care unit, *LOS* length of stay in days

^aFailed CMV was defined as requiring a non-conventional therapy such as ECMO, NO, or HFOV (note that some patients had more than one nonconventional therapy)

^bData for secondary outcomes are mean±S.D.

^cCharges in thousands of dollars

Table 28.5 Post hoc analysis of patient outcomes as a function of direct versus indirect lung injury in the Infasurf® (calfactant) study of Willson et al. (2005) in children with ALI/ARDS

	Placebo	Calfactant	P value
<i>Direct lung injury</i> (# patients)			
OI ↓ 25 %	31 %	66 %	0.0006
Ventilator days	17±10	13±9	0.05
Died	38 %	8 %	0.0005
<i>Indirect lung injury</i> (# patients)			
OI ↓ 25 % +	41 %	37 %	0.79
Ventilator days	17±10	18±10	0.75
Died	33 %	41 %	0.65

Data from Lopez-Herce et al. (1999)

OI ↓ 25 % = a decrease of 25 % or more in oxygenation index as a measure of improvement in the severity of respiratory failure; ventilator days = days on mechanical ventilation

This ongoing study is a prospective, masked randomized controlled trial of calfactant *versus* placebo in children and adults with ALI/ARDS

from “direct” lung injury in more than 30 centers in the USA, Canada, Korea, Israel, Australia, and New Zealand.

Exogenous surfactant has also recently been used successfully after lung transplant in both adults and children. A randomized controlled trial by Amital et al. (2008) in 42 adult patients after lung transplant showed that calfactant surfactant-treated patients had better oxygenation, less post-graft dysfunction, shorter ICU stay, and improved lung function at 1 month. This study followed multiple case reports showing clinical improvements from exogenous surfactant therapy after lung transplantation (Kermeeen et al. 2007; Della Rocca et al. 2002; Struber et al. 1999, 2007).

None of the studies of surfactant therapy in ALI/ARDS described in this chapter have identified any adverse long-term side effects in patients, particularly those with direct pulmonary forms of lung injury. The transient hypoxia and hemodynamic instability that typically surround surfactant instillation in severely ill patients have previously been well described in newborns with IRDS and have repeatedly been shown not to adversely impact long-term outcomes. The risk of transmission of infectious agents such as prions from the use of animal-derived surfactants cannot completely be ruled out, although it is greatly reduced by the organic solvent extraction methods used to prepare such drugs (synthetic surfactants have no risk of prion transmission). No meaningful systemic toxicities or side effects of animal or synthetic exogenous surfactants have been identified in a quarter century of use in newborn infants. Exogenous surfactant chemical components (phospholipids and proteins) are largely recycled in the lungs, and it is unlikely that the current FDA risk status of “no contraindications” for the newborn use of surfactant drugs will need to change for applications in older patients with ALI/ARDS.

In the absence of definitive data from controlled clinical trials, exogenous surfactant therapy is often used in practice as a “rescue” intervention when conventional therapies fail. However, experience from studies of surfactant therapy in neonates indicates that rescue therapy will be less helpful than treatment earlier in the

clinical course (e.g., Bevilacqua et al. 1996; Kattwinkel et al. 1993; Kendig et al. 1991, 1998; OSIRIS Collaborative Group 1992). A major conceptual benefit of surfactant therapy in ALI/ARDS is to enhance lung function and reduce the need for positive pressure mechanical ventilation that can otherwise worsen inflammation and cause iatrogenic lung injury. Administering surfactant late in the course of respiratory failure after prolonged mechanical ventilation has already occurred precludes this potential benefit. Evolving evidence documenting benefits for the most active exogenous surfactants in pediatric and/or adult patients with direct pulmonary ALI/ARDS will hopefully allow earlier and better-targeted use of this intervention in the future.

Finally, a major issue regarding the most optimal use of surfactant therapy in ALI/ARDS involves its combination with added agents or interventions that target other aspects of the complex pathophysiology of acute inflammatory lung injury. Combination therapy approaches may be particularly important in adults with ALI/ARDS, where responses to exogenous surfactant have so far been disappointing in terms of improving long-term outcomes. Combination therapies designed to exploit potential mechanistic synergy between surfactant and agents directed at different facets of lung injury may have a more substantial impact on long-term outcomes in patients with ALI/ARDS. The rationale for the use of exogenous surfactant therapy in specific combined-modality interventions for ALI/ARDS is described in more detail elsewhere (Raghavendran et al. 2008b; Notter et al. 2000; Pryhuber et al. 2005). Examples of agents that might be synergistic with exogenous surfactant in ALI/ARDS include vasoactive drugs such as inhaled nitric oxide, which has the potential to selectively enhance perfusion in newly ventilated lung regions recruited by exogenous surfactant (Raghavendran et al. 2008b; Notter et al. 2000; Pryhuber et al. 2005). Other drugs for possible use in combination with exogenous surfactant include anti-inflammatory antibodies or receptor antagonists, antioxidants, and antioxidant enzymes (Raghavendran et al. 2008b; Notter et al. 2000; Pryhuber et al. 2005). Specific

ventilator modalities or ventilation strategies that reduce iatrogenic lung injury may be equally important to consider in conjunction with surfactant therapy (Raghavendran et al. 2008b; Notter et al. 2000; Pryhuber et al. 2005).

Conclusions

Although exogenous surfactant replacement in premature infants with IRDS (hyaline membrane disease) was first attempted in the mid-1960s (Robillard et al. 1964; Chu et al. 1967) soon after the putative role of surfactant deficiency in this disease was identified, it took a generation longer for this therapy to actually be approved by the FDA for use in premature infants. Today lifesaving surfactant replacement therapy in premature infants is a crucial staple of neonatal intensive care. The development of surfactant replacement therapy for acute respiratory failure associated with lung injury (ALI/ARDS) has shared some of the same growing pains found in the case of IRDS, including the use of nonoptimal exogenous surfactants and delivery methods in initial controlled clinical trials. In addition, the complex multifaceted pathology of ALI/ARDS clearly presents more of a challenge for surfactant therapy compared to surfactant-deficient IRDS. It remains to be determined if the reversal of surfactant dysfunction in patients with ALI/ARDS will prove similarly lifesaving, despite the fact that a firm basic science rationale for exogenous surfactant therapy exists.

A functioning active lung surfactant film is required for successful respiration in humans and other air-breathing animals. Evidence is clear that endogenous surfactant becomes dysfunctional in direct forms of acute inflammatory lung injury, and exogenous surfactant therapy has been shown to mitigate lung injury severity in multiple animal models of ALI/ARDS. Treatment of humans with ALI/ARDS with exogenous surfactants in clinical studies has been associated with improved oxygenation and few side effects and has led to improved longer-term outcomes in several patient populations. In particular, surfactant

therapy has been documented to be beneficial in term infants with meconium aspiration lung injury, and it is also used in treating acute respiratory failure in neonatal pneumonia. Studies on surfactant therapy in children with direct pulmonary ALI/ARDS are also promising, with improvements found not only in lung function but also in longer-term variables (including survival in a recent study (Willson et al. 2005)). A substantial number of studies in adults with ALI/ARDS have also reported acute improvements in lung function (oxygenation) from surfactant therapy (Table 28.3). Lung functional improvements in principle have the potential to lower required ventilator distending pressures and reduce ventilator-induced lung injury and inflammatory cytokine production that can worsen patient outcomes. Significant statistical correlations have been demonstrated between acute improvements in lung function and improvements in clinically significant long-term outcomes in surfactant-treated infants with IRDS (Segeer et al. 1991; Kuint et al. 1994).

However, demonstrating improved long-term outcomes from exogenous surfactant therapy in patients with ALI/ARDS is complicated by several factors. These lung injury syndromes have a complex multifaceted pathophysiology that includes not only surfactant dysfunction but also prominent elements of inflammation, vascular dysfunction, and oxidant injury. In addition, progressive fibroproliferative lung injury may be present, as well as multiorgan pathology, particularly in patients with “indirect” or “extrapulmonary” ALI/ARDS. This multifaceted pathology reduces the resolving power of clinical studies to demonstrate beneficial effects on long-term outcomes from surfactant therapy, even if the intervention itself is effective in mitigating its targeted aspect of lung injury (i.e., surfactant dysfunction). Controlled trials in adults with ALI/ARDS have not yet shown that surfactant therapy can substantially improve long-term outcomes, although exogenous surfactants with the greatest content of highly active SP-B

have not been tested in detail in adults. Another major area that has received relatively little study in clinical trials to date is the use of exogenous surfactant therapy in combination with potentially synergistic agents or interventions that target additional aspects of the complex pathophysiology of acute inflammatory lung injury. This latter approach may ultimately be particularly important in obtaining the most substantial reductions in mortality and long-term morbidity for pediatric and adult patients with severe ALI/ARDS-related acute respiratory failure.

Essentials to Remember

- Lung surfactant is a complex mixture of phospholipids and proteins. Pharmaceutical surfactants deficient in any of these components, particularly in the surfactant-associated proteins B and C, are unlikely to be effective in ALI/ARDS.
- Animal and human data support that exogenous surfactant improves immediate lung function in ALI/ARDS but proof of longer-term efficacy requires further study.
- Surfactant dysfunction and inhibition occurs early in ALI/ARDS and much of subsequent injury is likely consequent to positive pressure ventilation of the surfactant-deficient lung. Consequently, as in treatment of infantile respiratory distress syndrome, if treatment is to be effective, it should be administered early.
- Side effects of surfactant therapy are limited to transient hypoxia and hypotension associated with instillation, as the drug is not systemically absorbed. Better methods of aerosol delivery in the future may obviate these side effects as well as allow administration in the non-intubated patient.
- At present, treatment of ALI/ARDS with exogenous surfactant remains experimental.

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29.1 Nitric Oxide

Robin H. Steinhorn

Educational Objectives

Understand the regulation and physiologic functions of the nitric oxide-cGMP signaling pathway during normal pulmonary development.

Describe dysregulation of NO production and signaling in common neonatal and pediatric pulmonary and cardiac diseases.

Determine the clinical utility of inhaled nitric oxide in pediatric pulmonary and cardiac disease by utilizing physiologic principles and clinical evidence.

29.1.1 Nitric Oxide Physiology

29.1.1.1 NO Physiology in the Normal Respiratory System

Nitric oxide (NO) is synthesized by the enzyme nitric oxide synthase (NOS) as a product of the conversion of l-arginine to l-citrulline. Three NOS isoforms are expressed in the lung, which are characterized by the regulation of their activities and by specific sites and developmental patterns of expression (Shaul 2002). Endothelial NOS (NOS3) is expressed in vascular endothelial cells and is the predominant source of NO production in the pulmonary circulation. Neuronal NOS (NOS1) and inducible NOS (NOS2) are both expressed in the airway epithelium and at low levels in the vascular smooth muscle. Furthermore, the expression of NOS2 can be induced in a variety of pulmonary cell types by exposure to endotoxin or inflammatory cytokines.

NOS is a complex oxidoreductase enzyme that functions physiologically as a dimer (Konduri and Kim 2009). A particularly important aspect for normal NOS function is sufficient availability of substrate (l-arginine) and cofactors. Interaction of eNOS with its critical cofactors such as heat shock protein 90, an intracellular molecular chaperone, and tetrahydrobiopterin, a bioactive form of folic acid, is necessary to facilitate NO production by eNOS (Landmesser et al. 2003). In contrast, depletion of these cofactors or inhibition of hsp90-eNOS interactions leads to “uncoupled” NOS activity, which promotes

release of the oxygen radical superoxide instead of NO. In addition to substrate and cofactors, NOS expression and activity are regulated by multiple other factors, including oxygen tension, hemodynamic forces, hormonal stimuli (e.g., estrogen), paracrine factors (e.g., VEGF), and reactive oxygen species (Grover et al. 2003; MacRitchie et al. 1997; Mata-Greenwood et al. 2006; North et al. 1996).

NO is a gas molecule that can diffuse freely from the endothelium to the vascular smooth muscle cell. The biologic effects of NO in vascular smooth muscle are mediated primarily through activation of soluble guanylate cyclase, which promotes conversion of GTP to cGMP (Fig. 29.1). cGMP relaxes vascular smooth muscle through activation of cGMP-gated ion channels and activation of cGMP-dependent protein kinase (PKG). However, recent studies indicate that alternative NO signaling pathways likely also exist through reaction of NO with protein thiols to form S-nitrosothiols (SNO), which may induce vasodilation or protein modification (Gaston et al. 2003).

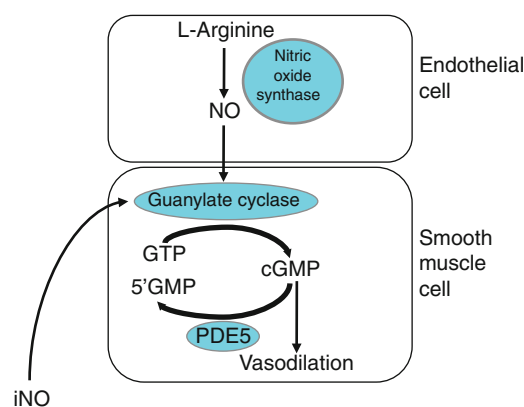


Fig. 29.1 Nitric oxide (NO) signaling pathways in the regulation of pulmonary vascular tone. NO is synthesized by nitric oxide synthase (NOS) from the terminal nitrogen of L-arginine. NO from endogenous sources, or delivered as an inhaled gas, stimulates soluble guanylate cyclase (sGC) to increase intracellular cGMP, which indirectly decreases free cytosolic calcium, resulting in smooth muscle relaxation. Specific phosphodiesterases such as PDE5 hydrolyze cGMP, thus regulating the intensity and duration of its vascular effects. Inhibition of cGMP-phosphodiesterases with agents such as sildenafil may enhance pulmonary vasodilation

NO is detectable in expired gas, and studies in both animals and humans suggest that the principle source of expired NO is the lung epithelium rather than the pulmonary vasculature (Shaul 2002). The functions of NO in the airway include neurotransmission, smooth muscle relaxation, and bacteriostasis, and also the modulation of mucin secretion, ciliary motility, and in the perinatal period, regulation of lung liquid production.

Phosphodiesterases serve to catalyze the breakdown of cGMP, and are therefore able to regulate the magnitude and duration of vasodilation observed in response to NO. Each family of PDEs has a distinct pattern of specificity for cAMP and/or cGMP, and each PDE isoform has specific tissue and cellular distributions (Soderling and Beavo 2000). The prevalent PDE within the lung is the cGMP-specific PDE5, although significant amounts of PDE1, PDE3, and PDE4 are also present (Maclean et al. 1997; Pauvert et al. 2002). As the primary enzyme responsible for regulating cGMP, PDE5 potentially represents the most important regulator of NO-mediated vascular relaxation in the normal pulmonary vascular transition after birth (Abman et al. 1990; Lakshminrusimha and Steinhorn 1999).

29.1.1.2 Developmental Regulation of NO Physiology

The fetus must maintain a state of pulmonary hypertension to survive and optimally use the oxygen provided from the placental circulation. Because the placenta, not the lung, serves as the organ of gas exchange, most of the right ventricular output crosses the ductus arteriosus to the aorta, and only 5–10 % of the combined ventricular output is directed to the pulmonary vascular bed. Pulmonary vascular constriction plays a key role in maintaining high pulmonary vascular tone during fetal life. There are multiple pathways involved in maintaining high pulmonary vascular resistance in utero, including hypoxia (a defining feature of fetal development), as well as endothelin-1 (ET-1), thromboxane, acidosis, and various mediators of inflammation (Lakshminrusimha and Steinhorn 1999). At the same time, the fetal lung and pulmonary vasculature must prepare for the dramatic adaptation to air breathing at the

time of birth. This complex orchestration of fetal and postnatal lung development is regulated in part by important maturational changes in expression and activity of nitric oxide synthase (NOS) isoforms.

Lung eNOS mRNA and protein is present in the early fetus and increases with advancing gestation and during the early postnatal period in multiple species (North et al. 1994; Parker et al. 2000). This increase in lung endothelial NOS content occurs at the same time the fetal pulmonary vasculature develops the capacity to respond to endothelium-dependent vasodilator stimuli, such as oxygen and acetylcholine (Tiktinsky and Morin 1993). Recent data indicate that low fetal NOS activity may be maintained during fetal life in part through increased levels of asymmetric dimethyl arginine (ADMA), an endogenously produced arginine analogue that acts as a competitive NOS inhibitor (Arrighoni et al. 2003; Pierce et al. 2004).

The neuronal and inducible NOS isoforms have been also been identified in the fetal lung of multiple species and appear to be primarily localized to the airway epithelium. Their expression and activity appear to be similarly regulated in specific developmentally driven patterns (Rairigh et al. 1998; Shaul et al. 2002; Sherman et al. 1999; Tzao et al. 2000). Similar to vascular NO, epithelial NO production increases during the third trimester and occurs in parallel with rises in nNOS and eNOS expression in the proximal lung (Shaul et al. 2002). NO is now recognized as important to epithelial development and function during lung development and appears to regulate critical functions such as lung liquid clearance by the respiratory epithelium at the time of birth (Cummings and Wang 2001), an essential component of the transition of the fetus to air breathing. Epithelium-derived NO is also critical to the regulation of bronchomotor tone in the early newborn period, playing an important role in the opposition of airway contraction (Steinhorn and Martin 2002).

Dramatic cardiopulmonary events at birth facilitate the transition to gas exchange by the lung; these include a rapid fall in pulmonary vascular resistance and pulmonary artery pressure

and a tenfold rise in pulmonary blood flow. Birth-related stimuli, such as ventilation, increasing oxygen tension, and increasing shear stress serve to acutely increase NOS activity and NO production. Acute or chronic inhibition of NOS in fetal lambs produces pulmonary hypertension following delivery, indicating the fundamental importance of endogenous NO-cGMP signaling in the normal pulmonary vascular transition (Abman et al. 1990; Fineman et al. 1994). Additional data from human infants also indicate that sufficient supplies of the NOS substrate L-arginine are necessary for optimal NOS function during the neonatal period (Pearson et al. 2001).

The enzymes responsible for the downstream vascular responses to NO are also developmentally regulated. Soluble guanylate cyclase, which produces cGMP in response to NO activation, is expressed and active by late gestation (Bloch et al. 1997). Interestingly, the developmental patterns of PDE5 expression are not as clearly defined as for NOS and sGC. For instance, in rats, PDE5 expression and activity steadily increase through the end of gestation, peak shortly after birth, and then drop dramatically into adulthood. In contrast, in neonatal lambs, PDE5 activity and expression acutely decrease at birth and then rise again at 4–7 days of life (Farrow et al. 2010; Hanson et al. 1998a; Okogbule-Wonodi et al. 1998; Sanchez et al. 1998).

29.1.1.3 Dysregulation of Nitric Oxide Production and Response in the Diseased Respiratory System

General Concepts of NO-cGMP Dysregulation in Pulmonary Vascular Disease

Decreased expression of nitric oxide synthase and its downstream effectors, such as soluble guanylate cyclase and protein kinase G, contributes to vascular dysfunction in a number of pulmonary diseases. In addition, insufficient substrate or abnormal interactions with cofactors can lead to NOS dysfunction through “uncoupling” of the enzyme, even when protein levels are preserved. Furthermore, there is increasing awareness that a primary mechanism for the loss of bioavailable

NO is its interaction with oxygen radicals such as superoxide. If levels of superoxide ($O_2^{\cdot-}$) rise, NO can combine with it in a reaction which is diffusion limited and many times faster than dismutation of $O_2^{\cdot-}$ by superoxide dismutases (Beckman and Koppenol 1996). This reaction not only reduces bioavailable NO; it also produces the potent oxidant, peroxynitrite ($ONOO^-$), which can nitrate target proteins, such as guanylate cyclase or K^+ channels, preventing their activation by NO or other physiologic signals. Increased expression and/or activity of cGMP-phosphodiesterases can also disrupt NO-cGMP signaling, and recent data indicate that increased levels of reactive oxygen species rapidly activate PDE5 activity and expression (Farrow et al. 2008a, 2010, 2012).

Persistent Pulmonary Hypertension

Neonatal respiratory failure affects 2 % of all live births and is responsible for over one third of all neonatal mortality. Pulmonary hypertension complicates the course of more than 10 % of all neonates with respiratory failure, and the most severe PPHN has been estimated to occur in 2 per 1,000 of live-born term infants (Walsh-Sukys et al. 2000). Even with appropriate therapy, the mortality for moderate–severe PPHN remains just under 10 %, and up to 25 % of surviving infants have evidence for long-term neurodevelopmental disability (Steinhorn 2008, 2010).

PPHN occurs in association with a diverse group of illnesses but can be generally characterized as one of three types: (1) the abnormally constricted pulmonary vasculature due to lung parenchymal diseases such as meconium aspiration syndrome, respiratory distress syndrome, or pneumonia; (2) the lung with normal parenchyma and remodeled pulmonary vasculature, also known as idiopathic PPHN; or (3) the hypoplastic vasculature as seen in congenital diaphragmatic hernia. While “pure” idiopathic pulmonary hypertension occurs in the minority (~20–25 %) of infants with PPHN, severe cases are almost certainly affected by both parenchymal and vascular disease. Severe, early pulmonary vascular disease is believed to be the result of antenatal

events that lead to significant pulmonary vascular remodeling in utero (Geggel and Reid 1984).

Because of the inherent difficulties in studying the pulmonary vasculature in the fetal and neonatal period, much of the knowledge about alterations in NO-cGMP signaling has been derived from animal models. Ligation or constriction of the fetal ductus arteriosus results in rapid antenatal remodeling of the pulmonary vasculature, which has been extensively studied in the neonatal lamb. After birth, ductal ligation lambs exhibit the increased fetal pulmonary artery pressure, severe hypoxemia, and high mortality, characteristic of human PPHN. Decreased expression of eNOS mRNA and protein and diminished eNOS activity have been documented in umbilical venous endothelial cells isolated from infants with PPHN as well as in pulmonary vascular tissue from the ductal ligation lamb model (Shaul et al. 1997; Villanueva et al. 1998). There is increasing evidence that reactive oxygen species produced by vascular NADPH oxidase and other sources likely contribute to suppressed NOS expression and may also interfere with NOS activity through inhibiting tetrahydrobiopterin synthesis (Brennan et al. 2003; Farrow et al. 2008b). Recent studies have confirmed decreased hsp90-eNOS association in PPHN lambs, which promotes “uncoupled” eNOS activity that could further amplify superoxide production (Konduri et al. 2007a). Expression and activity of vascular soluble guanylate cyclase are diminished in PPHN lambs (Steinhorn et al. 1995), and activity of PDE5 is increased (Farrow et al. 2010; Hanson et al. 1998b), both of which promote decreased cGMP concentrations (Tzao et al. 2001).

There is also mounting evidence that oxidant stress from mitochondria and NADPH oxidase isoforms plays a central role in the antenatal events that culminate in the PPHN phenotype (Afolayan et al. 2012; Wedgwood et al. 2013). New data raise the possibility that current therapeutic practices also play an important role in promoting postnatal oxidant stress, abnormal pulmonary vascular reactivity, and vascular remodeling. In particular, the use of high concentrations of therapeutic oxygen has recently become controversial in numerous settings. Hyperoxic ventilation is assumed to

facilitate pulmonary vasodilation and thus remains a mainstay in the treatment of PPHN. However, surprisingly little is known about what oxygen concentrations will maximize benefits and minimize risk. The extreme hyperoxia routinely used in PPHN management may in fact be toxic to the developing lung by the formation of reactive oxygen species such as superoxide and reduced activity of endogenous antioxidants (Farrow et al. 2008b; Wedgwood et al. 2011). New data indicate that even brief periods of exposure to 100 % O₂ increase reactivity of normal and remodeled pulmonary vessels (Lakshminrusimha et al. 2006a, 2007a, 2009a), diminish the response of the pulmonary vasculature to endogenous and exogenous nitric oxide (Lakshminrusimha et al. 2007b), and increase activity of cGMP-specific phosphodiesterases (Farrow et al. 2008a, 2010, 2012).

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) is a serious birth defect defined as abnormal development of the diaphragm. Severe CDH develops early in the course of lung development, and as a result, airway divisions, alveolarization, and vascular branching are significantly disrupted. Due to the complexity of their disease, mortality for infants with CDH remains very high (30–40 %) and has not changed significantly over the past few decades despite medical advances that have improved outcomes for other neonatal respiratory diseases.

Several investigators have utilized autopsy material to explore the role of NOS expression in infants that died of CDH, but results have yielded inconsistent answers (Shehata et al. 2006; Solari et al. 2003). Others have utilized animal models of CDH, including exposure of fetal rats to the herbicide nitrofen, and surgical creation of a diaphragmatic defect in fetal lambs. Results have again varied, with some groups showing decreased vs. normal eNOS expression in CDH. Recent data showed that treatment with exogenous NO enhanced lung branching and growth in lung explants from nitrofen-exposed rat fetuses, which suggests that even when NO expression is normal, NO production or bioavailability may be reduced (Muehlethaler et al. 2008). Abnormalities

in downstream signaling mechanisms also occur, including decreased pulmonary artery relaxations to NO donors or cGMP analogues, possibly due to increased PDE5 expression or activity (Vukcevic et al. 2005).

Bronchopulmonary Dysplasia

In the United States alone, more than 10,000 babies develop bronchopulmonary dysplasia (BPD) each year, a serious disease characterized by persistent abnormalities of lung structure, including abnormal vascular growth and impaired alveolarization. Mice deficient in eNOS have abnormal lung architecture at birth, suggesting a critical role for NO in early lung development. New evidence indicates that impaired production of endogenous NO contributes to the pathogenesis of BPD, with multiple studies demonstrating that exhaled NO, as well as lung epithelial eNOS and nNOS expression, are decreased in models of BPD induced by prematurity (Afshar et al. 2003). Exposure of neonatal rats to hyperoxia produces alterations in lung alveolarization and vascularization similar to BPD. Increases in NOS expression have been observed in the hyperoxia model, although some have suggested that NOS dysfunction may contribute to its pathophysiology, perhaps due to inadequate substrate (Vadivel et al. 2010). Exogenous NO or sildenafil given during the recovery period improves growth of lung parenchyma and blood vessels, supporting this theory (Ladha et al. 2005; Lin et al. 2005).

Congenital Heart Disease

Infants with congenital heart lesions associated with increased pulmonary blood flow, such as truncus arteriosus or atrioventricular canal, will develop progressive vascular remodeling and secondary pulmonary hypertension. These children, as well as infants that undergo surgical correction in the first week of life, are at risk for significant postoperative pulmonary hypertension. A lamb model has been used to delineate how chronic increases in pulmonary blood flow after birth alter pulmonary vascular development. Aortopulmonary graft shunts are placed prior to birth in lambs, a model that mimics the human patterns of excessive postnatal pulmonary blood

flow and produces slowly progressive changes in NO-cGMP signaling. By 4 weeks of age, eNOS mRNA and protein are increased, but NO-mediated dilation is diminished. This seems to be due in part to “uncoupling” of NOS, such that superoxide rather than NO is produced (Lakshminrusimha et al. 2007b; Steinhorn et al. 2001). By 4 weeks, PDE5 expression is also increased, representing another mechanism that may inhibit NO-cGMP-mediated vasodilation (Oishi et al. 2007). Acute changes in pulmonary vascular reactivity can arise following surgical correction of CHD, especially if functional or structural vascular responses to excessive pulmonary blood flow have occurred.

29.1.2 Inhaled Nitric Oxide

Inhaled nitric oxide (iNO), initially approved for clinical use in neonates with hypoxemic respiratory failure in 1999, has been one of the most significant advances in neonatal intensive care. Its use has now extended to other pediatric populations with pulmonary hypertension or other respiratory illness. Inhaled NO is well suited for the treatment of pulmonary hypertension: it is a rapid and potent vasodilator that can be delivered as inhalation therapy to airspaces approximating the pulmonary vascular bed. NO that reaches the blood stream binds avidly to hemoglobin, which further localizes its effect to the lung vasculature. Inhaled NO can also improve oxygenation by redirecting blood from poorly aerated or diseased lung regions to better-aerated distal air spaces, thus improving ventilation/perfusion matching. In contrast, intravenous dilators such as prostacyclin, tolazoline, and sodium nitroprusside often produce nonselective effects, leading to systemic hypotension, worsening ventilation/perfusion matching, and impaired oxygenation.

29.1.2.1 Delivery Methods and Interactions with Mechanical Ventilation

NO is a colorless and odorless gas; delivery systems must minimize contact of NO with oxygen to prevent formation of the toxic gas NO₂. In

early studies, nitric oxide was delivered by relatively simple two-stage regulators that introduced the gas into the circuit of continuous flow ventilators and measured inhaled concentrations of nitric oxide and its oxidative products at the endotracheal tube by chemiluminescence analyzers (Roberts et al. 1997). While inexpensive and relatively reliable, these methods lacked alarm systems to detect gas delivery outside the intended range. Currently, in most parts of the world, NO gas and delivery systems are provided by a single manufacturer (Ikaria Inc, Clinton, NJ). Available devices deliver consistent NO concentrations in the range of 0–80 ppm in a wide range of ventilator systems, including those that do not use continuous flow throughout the inspiratory/expiratory cycle. They also maintain continuous integrated monitoring using electrochemical NO/NO₂ alarm sensors.

There are relatively few contraindications to iNO, which mainly consist of congenital heart disease with left ventricular outflow tract obstruction, such as interrupted aortic arch, critical aortic stenosis, and hypoplastic left heart syndrome. A relative contraindication is severe left ventricular dysfunction. These children are likely to have pulmonary venous hypertension due to high left atrial pressures, and use of iNO may aggravate pulmonary edema unless there is also optimization of cardiac performance.

The available evidence best supports the initiation of iNO at a dose of 20 ppm. Early studies in animals and infants used iNO doses as high as 80–100 ppm (Roberts et al. 1997). However, large clinical trials showed inhalation of higher iNO doses produced no better outcomes than lower doses of 20 ppm (Neonatal Inhaled Nitric Oxide Study Group 1997b), and sustained treatment with 80 ppm NO increased the risk of methemoglobinemia (Davidson et al. 1998). Pulmonary arterial pressure was measured in neonates with persistent pulmonary hypertension exposed to 0–40 ppm iNO, and revealed that optimal improvement in the pulmonary-to-systemic arterial pressure ratio was observed at an NO dose of 20 ppm (Tworetzky et al. 2001).

Severe parenchymal lung disease may be associated with poor responsiveness to iNO in

newborns with PPHN. In newborns with severe lung disease, high-frequency oscillatory ventilation (HFOV) is frequently used to optimize lung inflation and minimize lung injury. The combination of HFOV with iNO often enhances the improvement in oxygenation in newborns with severe PPHN complicated by diffuse parenchymal lung disease and underinflation. A randomized, multicenter trial demonstrated that when PPHN was complicated by severe lung disease, response rates for HFOV + iNO were better than HFOV alone or iNO with conventional ventilation (Kinsella et al. 1997). Improved responses to combined treatment with HFOV + iNO likely reflect reduced intrapulmonary shunting as well as augmented NO delivery to its site of action.

During iNO therapy, adequate oxygen saturation and hemoglobin levels should be maintained to provide appropriate oxygen delivery. Once oxygenation and perfusion targets are achieved, a stable response to iNO should be followed by efforts to wean both iNO and FiO_2 . Inhaled NO can usually be easily weaned to 5 ppm within 24 h, and further weaning and discontinuation of iNO can generally be accomplished in 4–5 days.

Discontinuation of iNO is typically attempted once the FiO_2 is weaned to <0.40 – 0.60 and the PaO_2 is >60 . Mild or transient decreases in PaO_2 necessitating an increase in inspired oxygen are sometimes seen after discontinuation, but are generally well tolerated. However, stopping iNO can be complicated by “rebound pulmonary hypertension,” a more dramatic worsening of hypoxemia that responds only to reinstitution of iNO. Rebound pulmonary hypertension is more likely to be observed in infants exposed to higher iNO doses for several days and can usually be avoided by stepwise weaning to 1 ppm prior to discontinuation. Prolonged need for iNO therapy should lead to further evaluation to determine whether previously unsuspected anatomic lung or cardiovascular disease is present, such as pulmonary venous stenosis, alveolar capillary dysplasia, or severe lung hypoplasia.

A recent study evaluated the role of delivering iNO noninvasively, by nasal cannula, in newborns with prolonged pulmonary hypertension due to congenital diaphragmatic hernia (Kinsella

et al. 2003). This study not only established the feasibility of this approach but also found that nasopharyngeal NO concentrations were approximately 50 % of the NO levels measured proximally in the delivery device. While development of a pulsed delivery system has been attempted, it has not reached broad-based use, which currently confines the use of iNO to the hospital setting.

29.1.2.2 Side Effects and Safety Issues

The reaction of NO with oxygen produces NO_2 , which is highly toxic to pulmonary epithelial cells. Current delivery devices measure NO_2 continuously using electrochemical cells, so toxic levels can be avoided. After inhalation, NO diffuses into the bloodstream and rapidly reacts with oxyhemoglobin to form methemoglobin (metHb) and nitrate. Activity of methemoglobin reductase is often reduced in the neonatal period, and high levels of methemoglobin could aggravate hypoxia. Methemoglobin levels should be followed closely in the first few hours of therapy and then at 24-h intervals. Fortunately, NO_2 levels higher than 2 ppm and methemoglobin levels higher than 5 % have generally been reported only in infants receiving high doses of iNO, in the range of 80 ppm (Davidson et al. 1998). An additional concern is that NO increases platelet cGMP, which inhibits platelet aggregation and could theoretically increase bleeding complications. While iNO increases bleeding time in healthy adults (Hogman et al. 1993), bleeding complications, including intracranial hemorrhage, have not been increased in infants treated with iNO.

Inhaled NO is usually delivered with high concentrations of oxygen. While hyperoxic ventilation is used to promote pulmonary vasodilation in PPHN, there is little to indicate that increasing oxygen concentrations beyond greater than 50–60 % further enhances pulmonary vasodilation in the normal or remodeled pulmonary circulation (Lakshminrusimha et al. 2007a, 2009a, 2011). High concentrations of oxygen may be toxic to the developing lung through formation of reactive oxygen species, such as superoxide anions (Lakshminrusimha et al. 2006b, 2011). Superoxide may combine with NO to form

Table 29.1 Summary of the large, multicenter randomized trials of inhaled NO in term newborns with hypoxemic respiratory failure and/or PPHN, showing the effect of iNO on ECMO utilization and mortality

	<i>n</i>	Initial OI	% ECMO		% Mortality	
			Control	iNO	Control	iNO
NINOS (1997b)	235	44	55	39 ^a	17	14
Roberts et al. (1997)	58	44.4	71	40 ^a	7	7
Clark et al. (2000)	248	39	65	48 ^a	8	7
Davidson et al. (1998)	155	24.7	34	22	2	8
Konduri et al. (2004b)	299	19.2	12	10	9	7

Adapted from Konduri (2004a)

^aDenotes significant reduction ($p < 0.05$)

peroxynitrite (Lakshminrusimha et al. 2006b), a particularly potent oxidant with the potential to produce vasoconstriction, cytotoxicity, and damage to surfactant proteins and lipids.

One potential concern is that use of iNO could delay initiation of extracorporeal support (ECMO), which is the only therapy proven to decrease PPHN mortality. Fortunately, a recent review of registry data from the Extracorporeal Life Support Organization found that use of iNO did not significantly delay initiation of extracorporeal support (ECMO) or negatively influence survival in neonates that require ECMO (Fliman et al. 2006). However, in centers that do not have immediate availability of ECMO support, use of iNO in the neonatal period must be approached with caution. Inhaled NO cannot be abruptly discontinued because rebound pulmonary hypertension is likely (Davidson et al. 1998), therefore transport with iNO is needed if referral for ECMO is necessary. This capability should be determined in collaboration with the ECMO center before iNO treatment is started. The use of iNO with high-frequency ventilation creates particular problems for transport, and transport strategies should be considered before these therapies are combined in a non-ECMO center.

29.1.2.3 Indications and Outcome Analysis

PPHN

Large, multicenter placebo-controlled trials have established the safety and efficacy of iNO in neonates with severe persistent pulmonary hypertension, as defined by an oxygenation index (OI; calculated as (mean airway pressure $\times$ $\text{FiO}_2 \times 100$)/

PaO_2) of >25 . These studies provided clear evidence that iNO acutely improves oxygenation and significantly decreases the need for ECMO support in newborns with diverse causes of hypoxemic respiratory failure and/or PPHN, as shown in Table 29.1 (Clark et al. 2000; Neonatal Inhaled Nitric Oxide Study Group 1997b). While these studies paved the way to FDA approval, it is equally important to note that iNO did not reduce the mortality, length of hospitalization, or the risk of significant neurodevelopmental impairment associated with PPHN (Clark et al. 2003; Neonatal Inhaled Nitric Oxide Study Group 2000). Moreover, a subsequent multicenter trial studied the potential benefit of beginning iNO at a milder or earlier point in the disease course (for an oxygenation index of 15–25). Early use of iNO did not decrease the incidence of ECMO and/or death, improve other patient outcomes, or reduce the incidence of severe neurodevelopmental impairment (Konduri et al. 2004b, 2007b).

These clinical trials also revealed that as many as 40 % of infants will not respond or sustain a response to iNO. The reasons for an inadequate response are diverse and require the clinician to carefully analyze the relative roles of parenchymal lung disease, pulmonary vascular disease, and cardiac dysfunction for each infant. For instance, if severe airspace disease is associated with PPHN, strategies such as high-frequency ventilation that optimize lung expansion are likely to be effective, and the two therapies used together are more effective than either used individually (Kinsella et al. 1997).

While initial case reports suggested that iNO improved oxygenation in infants with congenital

Table 29.2 Randomized, masked trials of iNO for prematurity and respiratory failure

	Patients enrolled	Gestational age (weeks)	Birth weight (g)	Age at study entry	Initial dose	Duration of treatment	BPD risk reduction
Schreiber et al. (2003)	207	27.2	983	13 h	10 ppm	7 days	0.77 [0.6–0.98] ^a
Van Meurs et al. (2005)	420	26.0	838	26 h	5 ⇒ 10 ppm	76 h	0.97 [0.86–1.06]
Kinsella et al. (2006)	793	25.6	792	30 h	5 ppm	14 days	0.95 [0.87–1.03]
EuNO (2010)	800	26.5	~850	<26 h	5 ppm	21 days	1.05 [0.78–1.43]
Ballard et al. (2006a, b)	582	26.0	763	16 days	20 ppm	24 days	0.89 [0.78–0.99] ^a

^aDenotes significant reduction ($p < 0.05$)

diaphragmatic hernia, the above multicenter trials demonstrated that early administration of iNO did not reduce death or ECMO utilization in CDH (Neonatal Inhaled Nitric Oxide Study Group 1997a). However, data from the registry maintained by the Extracorporeal Life Support Organization suggest that iNO decreases cardio-pulmonary arrest in infants with CDH that require ECMO (Fliman et al. 2006), which may improve later morbidity. Use of iNO in young, unstable infants with CDH should be accompanied by consideration for transfer to a center that can provide ECMO support.

Other Neonatal Respiratory Failure

Over the last decade, the use of iNO in the treatment of premature infants has been widely investigated as a preventative and rescue strategy. Early case reports of NO inhalation in premature newborns with severe respiratory failure demonstrated improvement in pulmonary hypertension, accompanied by marked improvement in oxygenation. Five large randomized, masked clinical trials focusing on iNO administration in preterm infants have now published their outcomes and include a wide range of patient populations, disease severity, and treatment strategies (Table 29.2).

Three of the trials used an early, protective strategy, randomizing infants to receive placebo gas or iNO for 7–21 days (Kinsella et al. 2006; Mercier et al. 2010; Schreiber et al. 2003). The smallest, single-center trial showed that iNO significantly improved survival without BPD (Schreiber et al. 2003), but this finding was not

confirmed in the two larger, multicenter trials. The trial conducted by Van Meurs et al. (2005) focused on an early rescue strategy by targeting infants with severe respiratory failure (mean oxygenation index of 22–23) and found that iNO did not reduce death or BPD. Furthermore, post hoc analysis of the 316 infants with birth weights of <1,000 g suggested the worrisome finding that iNO was associated with an increased risk of death and brain injury (grade 3 or 4 IVH or PVL).

Ballard et al. (2006a, b) studied the effects of iNO in older preterm infants still requiring mechanical ventilation, thus targeting a population at particularly high risk for BPD. In this trial, iNO was begun later (7–21 days), given at a higher dose (20 ppm, followed by stepwise weaning), and delivered for a longer time period (24 days). iNO administration resulted in a 23 % increase in survival without BPD at 36 weeks corrected gestational age. A follow-up study through 1 year of age showed that infants randomized to iNO were significantly less likely to require home oxygen or use bronchodilators, steroids, or diuretics after NICU discharge (Hibbs et al. 2008). Ballard's findings raise important questions about the timing and potential reversibility of lung injury, as well as whether higher doses or longer exposures to iNO are significant factors in supporting lung development. In addition, post hoc analysis indicated that African American infants were more likely to respond than Caucasians, raising interesting questions about the effect of race and ethnicity on response to iNO.

All three trials will continue to report neurodevelopmental outcomes through at least age 5. However, an NIH consensus statement and an individual patient meta-analysis concluded that iNO does not produce consistent improvements in pulmonary outcomes, survival, and neurodevelopmental outcomes in premature infants with respiratory failure (Askie et al. 2011; Cole et al. 2011). Inhaled NO can be lifesaving for preterm babies with pulmonary hypertension that is not due to parenchymal lung disease, as seen following prolonged rupture of membranes and/or oligohydramnios (Aikio et al. 2012). However, this disorder affects only 2 % of all preterm babies, which would create a substantial barrier to the conduct of a randomized clinical study (Ball and Steinhorn 2012). Further study is also needed to address the potential role for iNO in preterm infants managed with noninvasive modalities such as CPAP.

Pediatric Respiratory Failure

In initial clinical studies of adult and pediatric patients with severe acute respiratory distress syndrome (ARDS), inhaled NO produced selective pulmonary vasodilation and improved systemic oxygenation (Rossaint et al. 1993). However, subsequent randomized controlled trials have not shown any beneficial effect on mortality or duration of mechanical ventilation in pediatric or adult patients (Dobyns et al. 1999; Sokol et al. 2003). While a transient improvement in oxygenation was observed in most of these studies, it has been speculated that since most patients dying from acute respiratory distress syndrome suffer from multiple organ systems failure, lung-selective therapy such as inhaled NO may not improve the overall survival rate (Coggins and Bloch 2007).

In Primary and Secondary PHT

While iNO would theoretically benefit children with chronic primary or secondary pulmonary hypertension, its practical application is limited by its expense, lack of home-based continuous

delivery devices, and risk for rebound pulmonary hypertension. However, an important use of iNO has emerged for testing acute pulmonary vascular reactivity during cardiac catheterization. Inhaled NO has several advantages in this setting, including rapid onset of action and fewer potential adverse effects (e.g., systemic hypotension). For instance, Balzer et al. reported that the use of inhaled nitric oxide in combination with oxygen during preoperative evaluation allowed for identification of a greater number of appropriate candidates for corrective cardiac surgery or transplantation (Balzer et al. 2002). Others have shown that response to iNO during evaluation for pulmonary hypertension provides a safe, effective tool for predicting response to other agents such as calcium channel blockers and sildenafil.

One of the most common causes of secondary PHT in infants and children is bronchopulmonary dysplasia (Ivy et al. 2013; Mourani and Abman 2013). Mourani et al. demonstrated that the disease has a reactive component and that pulmonary pressures in patients with BPD improved to near-normal levels with acute exposure to iNO during cardiac catheterization (Mourani et al. 2004). However, the benefit of prolonged treatment with iNO in BPD-associated PH has not been well studied, mostly due to the logistical challenges of continuous long-term treatment.

Pulmonary hypertension after cardiopulmonary bypass can precipitate acute pulmonary hypertensive crises and contribute to excess morbidity and mortality after surgery for congenital heart disease. A number of small single-center studies indicate that iNO can attenuate pulmonary hypertension in at-risk postoperative patients, reduce the number of pulmonary hypertension crises, and shorten time on mechanical ventilation (Barr and Macrae 2010). In one larger randomized trial of pediatric patients, iNO (20 ppm) significantly decreased PVR and pulmonary hypertensive crises and shortened the time to extubation readiness (Miller et al. 2000).

Essentials to Remember

A complex set of enzymes including nitric oxide synthase, soluble guanylate cyclase, and phosphodiesterases control production of, and response to, nitric oxide in multiple lung cell types. Expression and activity of these enzymes change during fetal, neonatal, and pediatric development.

Persistent pulmonary hypertension of the newborn (PPHN) complicates the course of more than 10 % of all neonates with respiratory failure. Multiple abnormalities are now recognized in NO production and downstream signaling.

Inhaled nitric oxide (iNO) reduces need for extracorporeal support (ECMO) in PPHN but does not reduce mortality or improve long-term neurodevelopmental outcomes.

Several other pediatric diseases, including bronchopulmonary dysplasia and congenital heart disease, involve dysregulation of pulmonary NO-cGMP signaling pathways.

Inhaled nitric oxide is the optimal agent for assessing pulmonary vascular reactivity during cardiac catheterization. There may also be a role for iNO in the management of pulmonary hypertension after repair of congenital heart disease and for prevention of bronchopulmonary dysplasia in select populations of premature infants.

Poor responsiveness to iNO may result from inadequately treated parenchymal lung disease, poor cardiac function (particularly left ventricular dysfunction), or as a result of abnormal downstream signaling in remodeled pulmonary vessels.

Ventilation with high concentrations of oxygen may increase production of reactive oxygen species, such as superoxide anions, which can reduce vascular reactivity to iNO.

29.2 Nitric Oxide Pathway

Maurice Beghetti

Educational Objectives

- Describe the nitric oxide pathway and the potential therapeutic possibilities beyond inhaled nitric oxide.
- Describe the current use of phosphodiesterase inhibitors.

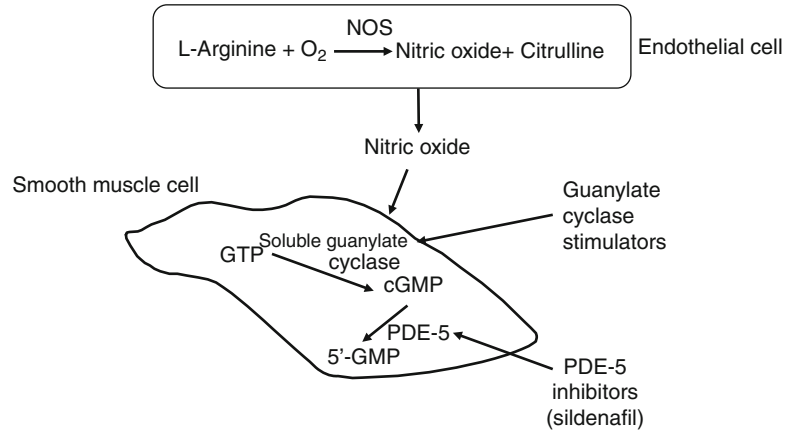
The nitric oxide pathway is an important regulator in the cardiovascular system and is present in vascular cells and platelets. Impairments of the nitric oxide/sGC/cGMP pathway provoke acute and chronic vascular injury, including endothelial dysfunction, vasoconstriction, and vascular remodeling in the pulmonary circulation. Inhaled nitric oxide produces selective pulmonary vasodilatation in well-ventilated lung regions by stimulating sGC and increasing cGMP in pulmonary vascular smooth muscle cells. However, the mode of delivery through inhalation as well as the very short half-life of inhaled NO led to the search of other mode of increasing cGMP levels and promoting pulmonary vasodilation and inhibition of smooth muscle cells proliferation.

Phosphodiesterase type 5 inhibitors, such as sildenafil and tadalafil, prevent the breakdown of cyclic GMP thereby raising cyclic GMP levels resulting in pulmonary vasodilation. Soluble guanylate cyclase stimulators may offer a new target for therapeutic intervention in pulmonary arterial hypertension by producing cGMP independently of nitric oxide.

29.2.1 Nitric Oxide Pathway

It has been well recognized that nitric oxide (NO) plays a major role in the cardiovascular system. The NO pathway is an important regulator in the

Fig. 29.2 Nitric oxide pathway. Abbreviations: NOS nitric oxide synthase, PDE-5 phosphodiesterase inhibitors



cardiovascular system and is present in vascular cells and platelets. Endothelial cell-derived NO, which acts in a paracrine fashion, is the endogenous stimulus of the soluble guanylate cyclase (sGC) (Fig. 29.2).

In the underlying smooth muscle cells and in platelets, NO activates the sGC, resulting in increased intracellular cyclic guanosine monophosphate (cGMP) levels, which induce vasorelaxation, inhibition of cell proliferation, and migration, by activating protein kinase C.

Impairments of the NO/sGC/cGMP pathway provoke acute and chronic vascular injury, including endothelial dysfunction, vasoconstriction, and vascular remodeling in the pulmonary circulation. As described before, inhalation of NO is used to treat subjects with pulmonary hypertension of various etiologies (Kinsella and Abman 2005). Inhaled NO produces selective pulmonary vasodilation in well-ventilated lung regions by stimulating sGC and increasing cGMP in pulmonary vascular smooth muscle cells. cGMP is the second messenger that indeed regulates contractility of smooth muscle cells through the modulation of kinases, phosphodiesterases, and ion channels. However, the mode of delivery through inhalation as well as the very short half-life of inhaled NO led to the search of other mode of increasing cGMP levels and promoting pulmonary vasodilation and inhibition of smooth muscle cells proliferation (see Sect. 29.1).

29.2.2 Phosphodiesterase Inhibitors

Keeping cGMP levels high in the smooth muscle cells would be of interest to sustain pulmonary vasodilation and inhibition of proliferation, and this may be obtained through the inhibition of the enzyme that degrades cGMP, the phosphodiesterase 5 (Ghofrani et al. 2004a). It has been shown that in pulmonary arterial hypertension (PAH), phosphodiesterase type 5 gene expression and activity are increased (Hanson et al. 1998b). Since the pulmonary vasculature is thought to contain substantial amount of PDE-5, the role of molecules acting on this enzyme is of major interest in pulmonary hypertension. Phosphodiesterase type 5 inhibitors prevent the breakdown of cyclic GMP thereby raising cyclic GMP levels resulting in pulmonary vasodilation (Croom and Curran 2008). All three PDE-5 inhibitors used in erectile dysfunction, such as sildenafil, tadalafil, and vardenafil, can cause significant pulmonary vasodilation (Ghofrani et al. 2004b).

Phosphodiesterase 5 inhibitors are as effective a pulmonary vasodilator as inhaled nitric oxide (Michelakis et al. 2002) and potentiate pulmonary vasodilation induced with nitric oxide (Abrams et al. 2000; Prasad et al. 2000). They may be particularly beneficial in conjunction with nitric oxide where withdrawal of nitric oxide may lead to rebound PAH (Atz et al. 2002; Namachivayam et al. 2006). In addition,

phosphodiesterase type 5 inhibitors may be sometimes preferred because they do not increase pulmonary wedge pressure. However, in some settings, they can sometimes worsen oxygenation and induce significant systemic vasodilation (Stocker et al. 2003).

29.2.2.1 Sildenafil

A significant number of uncontrolled studies have shown beneficial effect of sildenafil in diverse forms of PAH (Garg 2008; Mourani et al. 2009; Hrometz and Shields 2006; Saygili et al. 2004; Vida et al. 2007; Humpl et al. 2005; Noori et al. 2007). Sildenafil was indeed the first drug of this class and is still the most commonly used, particularly in young children with pulmonary arterial hypertension. Sildenafil can be used orally or intravenously but is currently only available orally. The efficacy of sildenafil has been shown to be the same when compared to nitric oxide on pre- and postoperative patients with elevated pulmonary vascular resistance undergoing cardiac surgery for congenital heart defects (Schulze-Neick et al. 2003). In addition to iNO, sildenafil has been shown to reduce significantly pulmonary artery pressure with no significant effect on systemic arterial or central venous pressure in children with PAH following cardiac surgery. But this remains controversial with others having shown systemic effects as well as VQ mismatch changes (Stocker et al. 2003). No significant dose effect was seen, a 0.5 mg/kg/dose every 4 h being as efficacious compared to a 2 mg/kg/dose (Raja et al. 2007). In neonates with PPHN associated with a congenital diaphragmatic hernia resistant to inhaled NO, sildenafil has been shown to improve cardiac output by reducing pulmonary hypertension (Noori et al. 2007). Recently, in a study assessing the effect of intravenous sildenafil in neonates with persistent pulmonary hypertension, it has been reported that intravenous sildenafil was well tolerated and induced acute and sustained improvements in oxygenation at the higher dose studied. In children with PAH, sildenafil has been shown to improve saturation and exercise

capacity without significant side effects (Karatza et al. 2005). Moreover, phosphodiesterase type 5 appears to be highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 with oral sildenafil has been shown to improve right ventricular contractility (Nagendran et al. 2007). The most relevant side effects of sildenafil include erections and systemic hypotension. The dose administered is 0.5–1 mg/kg/dose given three to four times a day, but some unpublished data suggest the need to raise to six times a day. While sildenafil has been approved for the treatment of functional class II–IV PAH adult patients, the data in children remain limited. Preliminary safety and efficacy trials are under way in pediatric patients, and results should be available very soon. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with PAH has been shown to be beneficial (Simonneau et al. 2008). Some reports have shown some synergistic effects also with prostanooids; this may be due to potential inhibition of phosphodiesterase type 3 induced by a cross talk with PDE5 (Ghofrani et al. 2003).

29.2.2.2 Tadalafil

Tadalafil is also a selective phosphodiesterase type 5 inhibitor with a longer duration of action (Affuso et al. 2006). Few data are available in children, but tadalafil has been shown to improve oxygenation in an animal model of newborn PAH (Tessler et al. 2008). In adults with severe PAH resistant to prostacyclin therapy, tadalafil has been used in addition to prostacyclin with some improvement in the functional class (Bendayan et al. 2008). The results of a randomized controlled adult trials (PHIRST-1) have shown beneficial effects on exercise capacity, symptoms, hemodynamics, and time to clinical worsening (Galie et al. 2009). The side effect profile is similar to sildenafil. The dose administered is 5, 10, 20, or 40 mg once daily. However, even if the drug has recently been approved for chronic treatment of PAH in adults, so far data on acute pulmonary hypertension and in pediatric patients are very limited.

29.2.3 Guanylate Cyclase Stimulators

Alterations of the nitric oxide receptor, soluble guanylate cyclase (sGC), may contribute to the pathophysiology of PAH (Fig. 29.2). Expression and activity of sGC are abnormal in animal models of persistent pulmonary hypertension of the newborn, and this may lead to abnormal response to administration of nitric oxide (Deruelle et al. 2005). Direct pharmacological stimulation of sGC, either alone or in combination with NO, may provide a novel approach for the treatment of pulmonary hypertension (PH). Moreover, in the presence of NO, it seems to enhance the effects of NO.

BAY 63-2521, also called now riociguat, is a novel, orally available compound that directly stimulates sGC and sensitizes it to its physiological stimulator, nitric oxide (Mittendorf et al. 2009; Evgenov et al. 2006). Upregulation of soluble guanylate cyclase in pulmonary arterial smooth muscle cells has been noted in human idiopathic PAH lungs (Schermulý et al. 2008). Stimulation of sGC may reverse right heart hypertrophy and structural lung vascular remodeling.

In a rat model of monocrotaline-induced pulmonary hypertension, chronic treatment with BAY 63-2521 significantly decreased RV/(LV+S) ratio, resulted in a significant reduction of fully muscularized arteries as compared to both monocrotaline groups, and increased the percentage of non-muscularized pulmonary arteries (Schermulý et al. 2008). Recently another guanylate cyclase stimulator, cinaciguat, has shown beneficial effects in a model of neonatal pulmonary hypertension (Chester et al. 2009).

The first results in adult patients have recently been reported showing that the drug was well tolerated and that it was superior to NO in efficacy and duration (Grimminger et al. 2009). However, it must be noted that the drug has significant systemic effects, and this may be taken into account in the future.

This group of drug clearly merit further investigation and may have a role in the treatment of acute pulmonary hypertension.

29.2.4 Others

Data with other molecules that can either improve nitric oxide production like L-arginine or act through the nitric oxide pathway such as citrulline are still under investigation. Results with L-arginine remain controversial, and there are no strong data to support its use currently (Pierce et al. 2004; Gorenflo et al. 2005; Souza-Silva et al. 2005; Beyer et al. 2008). Citrulline is currently under investigation, and some preliminary results in postoperative congenital heart surgery are of interest but clearly further studies are required (Barr et al. 2007; Ananthakrishnan et al. 2009).

There are single reports of other non-related molecules but no definite large-scale studies or use in children has been so far reported (Auten et al. 2007; Moya et al. 2002).

In conclusion, synergistic effects with inhaled NO or alternative to inhaled NO are under active research. Even if still not approved in pediatrics, the use of sildenafil a PDE5 inhibitor is largely reported, but further studies are required. The guanylate cyclase stimulators are also of particular interest, and we may have some reports in children in the next few years. Clearly, the nitric oxide pathway remains crucial in children with acute pulmonary hypertension.

Essentials to Remember

- There is a possibility to act on the NO-cGMP pathway beyond the administration of inhaled nitric oxide.
- Phosphodiesterase 5 inhibitors are largely used in clinical practice but are not approved, and further studies are required to define their use both for the indication and the dose.
- New compounds acting on the soluble guanylate cyclase are under development.
- Synergism between inhaled nitric oxide and either phosphodiesterase inhibitors or guanylate cyclase stimulators is an appealing concept.

29.3 Other Pulmonary Vasodilators and Newer Compounds

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Educational Objectives

- In pulmonary hypertension, endothelial dysfunction plays a major role. Endothelial dysfunction is characterized by an imbalance production of vasodilator such as nitric oxide and prostacyclin and vasoconstrictor such as endothelin-1.
- Different prostanoids including epoprostenol, iloprost, beraprost, and treprostinil can be used for the treatment of pulmonary hypertension.
- Endothelin receptor antagonists are of interest in different forms of pulmonary arterial hypertension. The role of these molecules in the treatment of pulmonary hypertension is discussed as well as new possibilities such as phosphodiesterase 3 inhibition and new molecules such as vasointestinal peptide.

It has been clearly demonstrated that in pulmonary hypertension, endothelial dysfunction plays a major role (Humbert et al. 2004). Endothelial dysfunction is characterized by an imbalance production of vasodilator such as nitric oxide and prostacyclin and vasoconstrictor such as endothelin-1. Nitric oxide and its pathway have been discussed in detail previously, but prostanoids and endothelin receptors antagonists have also been studied and used to treat pulmonary hypertension. Even if most of the reports are in chronic forms of the disease, they may have a role in the acute treatment or may be in the short-term treatment of some forms of increased pulmonary arterial pressure. It shows that there are other pathways than the nitric oxide pathway that can be addressed in pulmonary hypertension.

29.3.1 Prostanoids

Prostacyclin is a metabolite of arachidonic acid which is endogenously produced by the vascular endothelium. Prostacyclin acts through the binding of an IP receptor which is coupled to Gs proteins and activates adenylate guanylate cyclase to increase cAMP which in turns induces vasodilation and potentially inhibition of smooth muscle cells. cAMP acts indeed similarly to cGMP. Prostacyclin is a potent vasodilator in both the systemic and pulmonary circulation and has an antiplatelet activity (Jones et al. 1997). Pulmonary hypertension is characterized by an imbalance in the biosynthesis of prostacyclin and thromboxane A₂ (Christman et al. 1992). Likewise, children with severe PAH show diminished nitric oxide and prostacyclin synthase expression in the lung vasculature (Giaid 1998; Tuder et al. 1999). Prostacyclin has been used now for almost two decades and has been approved in 1995 for the treatment of severe chronic pulmonary arterial hypertension.

29.3.1.1 Epoprostenol

Epoprostenol has been shown to improve hemodynamics, quality of life, exercise capacity, and survival in adults and children with idiopathic pulmonary hypertension and pulmonary hypertension associated with other conditions (Rosenzweig et al. 1999; Barst et al. 1994, 1996, 1999; Sitbon et al. 2002; Yung et al. 2004). Epoprostenol lowers pulmonary artery pressure, increases cardiac output, and increases oxygen transport. Interestingly, the lack of an acute response may not preclude a chronic beneficial response, and an effect on reversing pulmonary vascular changes is raised (Barst et al. 1999). The development of a tolerance is possible, and some children need periodic dose escalation. The optimal dose of intravenous epoprostenol is unclear with a significant patient variability, and it is titrated incrementally with the most rapid increase during the first months. The dose is adjusted according to the response, and children usually need much higher doses than adults. In

adults, the mean dose is 20–40 ng/kg/min compared to a mean dose of 50–80 ng/kg/min in young children. Adverse effects are inhibition of platelet aggregation and adherence to the endothelium, systemic vasodilation, and hepatic enzymes alteration. Common side effects include diarrhea and jaw pain. Epoprostenol is chemically unstable at neutral pH and at room temperature and has a short half-life (1–2 min) rendering a continuous intravenous system with cold packs to maintain stability necessary. A central venous access is preferable as sudden interruption of the medication can lead to severe rebound pulmonary hypertension (Doran et al. 2008). However, if commonly used in chronic forms, the use of intravenous epoprostenol in acute pulmonary hypertension is nowadays seldom used as the intravenous administration may induce increase in ventilation perfusion mismatch and systemic hypotension, both being potential problems in intensive care patients. For this reason, alternate routes of delivery like inhaled, oral, and subcutaneous infusion are needed. Nevertheless, none of these alternate routes have proven to be as efficacious as intravenous epoprostenol.

29.3.1.2 Beraprost

Beraprost is an oral prostacyclin analogue. It is chemically stable and has a longer half-life (1 h), allowing for an oral utilization. Its potency is about half that of epoprostenol. Some studies have suggested that beraprost improves hemodynamics and survival in some forms of pulmonary hypertension (Saji et al. 1996; Nagaya et al. 1999). A study including some older children showed improved exercise capacity and symptoms for patients with pulmonary hypertension treated with oral beraprost compared to placebo (Galie et al. 2002; Barst et al. 2003a). Patients with idiopathic forms had a greater improvement than patients with pulmonary arterial hypertension associated with other disease. There was no difference in hemodynamics or functional class. Another study including children showed less disease progression at 6 months with beraprost compared to placebo (Barst et al. 2003a). Nevertheless, side effects like nausea, dizziness,

or headache are common and often limit dose increase. Several reports in Japan showed beneficial results in patients with congenital heart disease. Beraprost is currently only approved for the treatment of pulmonary hypertension in Japan and South Korea but neither in Europe nor in the USA. New oral prostanoids are currently studied in adults.

29.3.1.3 Iloprost

Iloprost is a prostacyclin analogue. The particular interest of iloprost is that it has been studied as an inhaled compound (Ewert et al. 2009). Iloprost is chemically stable and has a short biologic half-life (20–30 min). Iloprost is a potent pulmonary vasodilator with platelet aggregation inhibition properties (Kaukinen et al. 1984). One of the major advantages of the inhalative approach is its selectivity for the pulmonary vascular bed. This is of major importance when used in acute pulmonary hypertensive crisis with hemodynamic compromise characterized by low systemic pressure and low cardiac output. The minor effect on systemic pressure is here particularly beneficial. Moreover, its intrapulmonary selectivity may improve ventilation/perfusion mismatch and potentially oxygenation. Recently it has been suggested as an alternative to inhale nitric oxide for acute vasoreactivity testing (Jing et al. 2009).

Inhaled iloprost was first used in patients with acute respiratory failure and increased pulmonary arterial pressure accompanied by disturbances of gas exchange and then in acute heart right failure, and later effects were compared to inhaled nitric oxide (Zwissler et al. 1995a). All these different pathologies are encountered in pediatrics, and thus, these approaches have also been reported in children (Tissot and Beghetti 2009).

Several small studies have shown the potential efficacy of inhaled iloprost in the acute pulmonary hypertension setting in pediatrics such as acute lung injury, post-cardiopulmonary bypass (Hallioglu et al. 2003; Muller et al. 2003), in persistent pulmonary hypertension of the newborn (Ehlen and Wiebe 2003), or in chronic forms of pulmonary hypertension (Ivy et al. 2008).

De Luca et al. reported two neonates treated with inhaled iloprost for persistent pulmonary hypertension of the neonate, one with diaphragmatic hernia and one associated with an aneurysm of the vein of Galien (De Luca et al. 2007). Both patients were refractory to inhaled nitric oxide. Dose administered was 1 µg every 4 h. They showed improvement in oxygenation. Chotigeat et al. reported one case of persistent pulmonary hypertension of the neonate that had hypoxia despite high-frequency oscillation, inotropic drugs, and oral sildenafil (Chotigeat and Jaratwashirakul 2007). Aerosolized iloprost was given through the nasotracheal tube and induced significant improvement in oxygenation (Chotigeat and Jaratwashirakul 2007). Eifinger et al. treated four preterm neonates with 2 µg/kg iloprost per dose for a total of 44–65 doses in total. Oxygenation improved and echocardiography showed reduction in pulmonary pressure (Eifinger et al. 2008).

We are, however, still facing the same problem with these small case studies where no dose response or dose efficacy is reported and multiple different dosages are used, which does not allow to make recommendations for dose administration in this population. Moreover, these patients were on spontaneous ventilation or intubated and ventilated with different modes of ventilation, which increase the difficulty in assessing the dose delivered to the patient.

Some studies have also presented the use of inhaled iloprost in acute pulmonary hypertension after cardiopulmonary bypass for cardiac repair. Zwissler described the selective pulmonary vasodilatation of inhaled prostacyclin in a newborn after cardiopulmonary bypass (Zwissler et al. 1995b). However, no large-scale or randomized study has been performed in these settings, and it would be important to better assess the role of this therapy in pediatric acute pulmonary hypertension and compare with the use of inhaled nitric oxide. An important aspect in acute patients is that all information regarding dosage are available in non-intubated and with delivery systems mentioned above, and no real dose-finding studies or absorption studies have been conducted in

intubated patients. It is not known how much drug is delivered to the patient and how much may deposit in the nasotracheal tube, for example. As such caution should be the rule particularly in very young patients, and drug delivery in intubated patients should still be considered experimental. Studies should also aim at to determine the dose and mode of delivery particularly in intubated patients.

29.3.1.4 Treprostinil

Treprostinil is a prostacyclin analogue stable at room temperature and neutral pH with a longer half-life (about 3 h) compared to epoprostenol. Treprostinil is usually administered subcutaneously by continuous infusion and has been so far studied on chronic forms of pulmonary hypertension (Skoro-Sajer and Lang 2008). When given intravenously, treprostinil is associated with more prominent effects like headaches and leg pain compared to epoprostenol. Placebo-controlled trials have demonstrated improved exercise tolerance, clinical signs, symptoms, and hemodynamics in patients with PAH, including children (Simonneau et al. 2002). When transitioning from intravenous epoprostenol to intravenous treprostinil, children showed no change in exercise capacity (Ivy et al. 2007). Doses required are higher for intravenous treprostinil (1.5–4 times that of epoprostenol), requiring aggressive up-titration, but side effects are less. Unfortunately, when infused subcutaneously, discomfort at the infusion site with induration and sometimes ulceration of the skin is common. Intravenous use can also be a potential indication in children (Ivy et al. 2007; Barst et al. 2006a). The use of treprostinil in children can be considered for patients who have been on a stable dose of intravenous epoprostenol with clinical improvement. The role of treprostinil in acute forms of pulmonary hypertension remains to be studied. Clinical trials assessing inhalation and oral delivery of treprostinil are currently performed in adults, and recently inhaled treprostinil has received approval from the FDA for chronic forms of PAH but data in acute pulmonary hypertension are not available.

29.3.2 PDE-3 Inhibitors

As discussed for the nitric oxide pathway where PDE-5 inhibitors allow to maintain high levels of cGMP, the same can be applied to PDE3 and cAMP for the prostacyclin pathway (Fig. 29.3). Milrinone is a well-known and largely used drug in pediatric patients in particular after cardiac surgery (Hoffman et al. 2003; Chang et al. 1995). Several studies have shown its potential effect on the pulmonary vascular bed, and it has also been reported a synergistic effect with inhaled prostanooids giving to a combined application a special interest (Chang et al. 1995; Bassler et al.

2006; Lakshminrusimha et al. 2009b). This use in the acute pulmonary hypertension in intensive care unit definitely requires further studies as it may be of great help in some patients.

29.3.3 Endothelin Receptors Antagonists

Endothelin-1 is one of the most potent vasoconstrictor peptide produced primarily by the endothelial cell and has been implicated in the pathogenesis of pulmonary hypertension (Galie et al. 2004). Endothelin-1 expression and plasma levels are increased in patients with pulmonary hypertension and correlate inversely with prognosis. Two receptor subtypes, ET_A and ET_B, mediate the activity of endothelin-1 (Fig. 29.4). ET_A receptors are located on vascular smooth muscle cells and mediate vasoconstriction, whereas ET_B receptors are located on endothelial cells and cause endothelium-dependent vasodilation through the release of nitric oxide and prostacyclin, clearance of circulating endothelin-1 (Pollock et al. 1995; Hunley and Kon 2001; Cacoub et al. 1993). As for most of the other drugs discussed in this chapter, the use of endothelin receptor antagonist has mainly been studied in chronic forms of pulmonary vascular diseases.

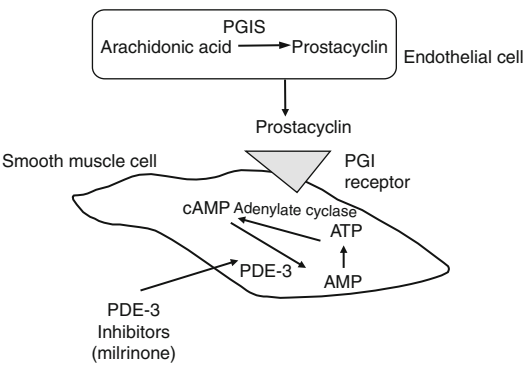


Fig. 29.3 Prostacyclin pathway. Abbreviations: PGI prostacyclin, PGIS prostacyclin synthase, PDE phosphodiesterase inhibitors

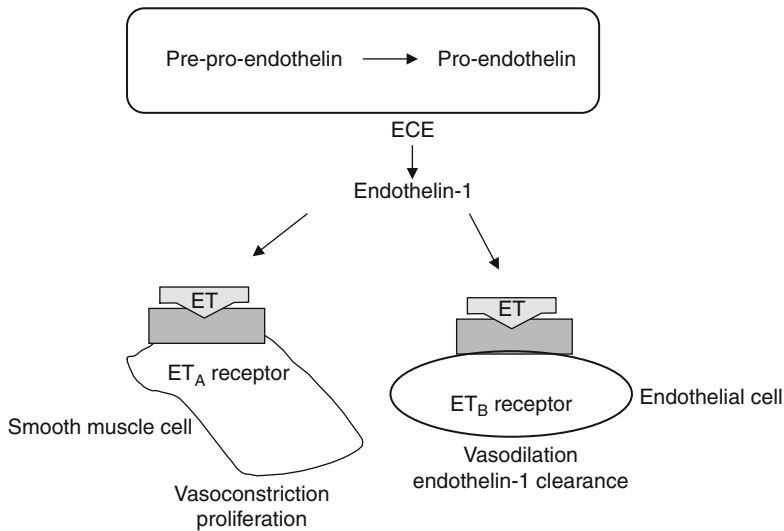


Fig. 29.4 Endothelin pathway

29.3.3.1 Bosentan

Bosentan is an oral dual endothelin receptor antagonist (Barst et al. 2004) and has been shown to improve exercise capacity, quality of life, and hemodynamics with lowering of pulmonary artery pressure and pulmonary vascular resistance in adults (Rubin et al. 2002; Channick et al. 2001) and in children with PAH (Rosenzweig et al. 2005; Maiya et al. 2006). Bosentan is approved since 2001 for the treatment of WHO functional class III and IV PAH patients ≥ 12 years old and for class II since 2008. In children with PAH related to congenital heart disease or with IPAH, bosentan lowers pulmonary artery pressure and pulmonary vascular resistance (Rosenzweig et al. 2005; Barst et al. 2003b). In children with PAH, bosentan has been shown to improve WHO functional class in about half of them. The risk for worsening PAH has been shown to be lower in children in WHO functional class I/II than in patients in WHO class III/IV at bosentan initiation. Bosentan is usually well tolerated in children in the dosing regimen of 31.25 mg bid for patients weighing 10–20 kg, 62.5 mg bid for those weighing 20–40 kg, and 125 mg bid for those weighing >40 kg. Bosentan has been successfully used in children on long-term epoprostenol therapy. Concomitant use of bosentan allowed for a decrease in epoprostenol dose and its associated side effects (Ivy et al. 2004). Risks associated with endothelin receptor antagonists therapy include hepatotoxicity [dose related], teratogenicity, and possibly male infertility (Beghetti et al. 2008). Liver function tests should be performed monthly. Elevated aminotransferases has been reported in 2.7 % of children compared to 7.8 % of patients ≥ 12 years. The discontinuation rate has been shown to be lower in children (14.4 %) compared to patients ≥ 12 years (28.1 %) (Beghetti et al. 2008). Bosentan may also decrease the effectiveness of warfarin therapy because of induction of CYP3A4 and CYP2C9. Currently, a specific pediatric formulation of bosentan is under investigation and has been approved for use in children by the European authorities.

29.3.3.2 Ambrisentan and Sitaxentan

Sitaxsentan and ambrisentan are selective ETA receptor antagonists with a high oral bioavailability and a long half-life (Channick et al. 2004). They block the vasoconstrictor effect of ETA receptors while maintaining the vasodilator effect and clearance function of ETB receptors. Sitaxentan has beneficial effects on exercise capacity and hemodynamics in patients with IPAH or PAH associated with connective tissue disease or congenital heart disease (Barst et al. 2006b) and also improves NYHA functional class. Sitaxsentan is usually administered orally at 100 mg bid. Significantly reduced dose of warfarin is needed to maintain a therapeutic INR. Ambrisentan has also been shown to improve exercise capacity and delay clinical worsening in PAH patients (Galie et al. 2005, 2008). Ambrisentan has been approved in 2007 for WHO functional class II–IV PAH patients. Both drugs are thought to affect the liver less than bosentan, and drug-to-drug interaction is probably less likely with ambrisentan. Further studies are needed in children.

In the particular setting of pulmonary hypertension after cardiac surgery, the role of the new therapies has raised interest (Beghetti 2004). In several animal and human studies, plasma endothelin-1 concentrations are consistently increased during and following cardiopulmonary bypass (Hiramatsu et al. 1997; Komai et al. 1993; Reddy et al. 1997). In a study of children with congenital heart disease, the plasma concentration of endothelin-1 3 h after cardiopulmonary bypass correlated with the degree of post-CPB pulmonary hypertension, suggesting a role for endothelin-1 in the pathophysiology of cardiopulmonary bypass-induced pulmonary hypertension (Schulze-Neick et al. 2002). In addition, several animal studies suggest that blockade of endothelin receptors attenuates post-cardiopulmonary bypass pulmonary hypertension and its associated altered reactivity. Thus, in lambs with preexisting pulmonary hypertension secondary to increased pulmonary blood flow, the increase in pulmonary vascular resistance following bypass was completely blocked in lambs pretreated with either dual or ET_A receptor antagonists (Petrosian

et al. 1999). In addition, the augmented pulmonary vascular reactivity following bypass, which is responsible for the potentially life-threatening acute increases in pulmonary vascular resistance, was also completely blocked in those lambs pretreated with endothelin receptor antagonists. A recent study showed that ET_A blockers might have a place in the therapeutic armamentarium (Ikonomidis et al. 2007).

Taking the particular situation of congenital heart surgery, where preoperative endothelial dysfunction exists in many instances, a further injury to the pulmonary endothelium due to ischemia reperfusion may explain the increased pulmonary vascular resistance occurring in some patients postoperatively.

29.3.4 Vasointestinal Peptide

Vasoactive intestinal polypeptide (VIP or aviptadil) has a potent vasodilative effect on pulmonary and systemic circulation. Continuous intravenous infusion of VIP appears to decrease PVR/SVR ratio in pulmonary hypertensive subjects, suggesting an overall pulmonary vasodilatory effect of VIP in pulmonary hypertension, and may become a new therapeutic agent in the future (Petkov et al. 2006; Leuchte et al. 2008; Said 2008; Said et al. 2007). The potential of this drug in acute forms is that it can be delivered by inhalation and has been shown to have acute effects on pulmonary arterial pressure even if modest and short-lived, but this led to a reduced workload for the right ventricle. In addition, aviptadil improved oxygenation in patients with significant lung disease. It clearly seems of interest to study this drug in acute and chronic forms of pulmonary arterial hypertension. Currently, a phase two trial is performed in which the acute effect of the drug during vasoreactivity testing is assessed.

The role of other drugs, currently studied in chronic forms of pulmonary arterial hypertension (statins, rho-kinase inhibitors, PDGF inhibitors, serotonin uptake inhibitors, etc.), has still to be defined in acute forms of PH.

Essentials to Remember

- There are several molecules like prostanooids, endothelin receptor antagonists, phosphodiesterase 3 inhibitors, and vasointestinal peptide besides the nitric oxide pathway that may play a role in the treatment of pulmonary hypertension in children both in the acute and the chronic settings.
- Further studies are needed before their introduction in the clinical setting to define and understand their role as well as the dose to deliver to young patients.

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30.1 Aerosol Drug Delivery During Pediatric Mechanical Ventilation

John Salyer

Educational Goals

- Understand the basics of aerosol characteristics.
- Describe the factors that affect aerosol delivery during mechanical ventilation.
- Describe the basic function of pneumatic nebulizers, vibrating mesh nebulizers, and metered-dose inhalers.
- Understand the relative effectiveness of these devices at delivering aerosols to the lung during mechanical ventilation.
- Describe the benefits of and clinical response to aerosolized bronchodilators during mechanical ventilation.

30.1.1 Introduction

Humans have been using the inhalational route for administering medication, both therapeutic and recreational for many centuries (Anderson 2005). The term inhaler was first used in the English literature in the eighteenth century (Sanders 2007; Rubin 2010). A great deal of creativity has gone into the naming of inhaler devices, some of which have deservedly been cast onto the ash heap of history including the volatilizer, varoma, vapo-haler, spirit burner, vapo-cresoline, pillow inhaler, atomizer, inspirator, pipe medicator, pulverisateur, and the ammoniaphone.¹ At one time, various forms of inhaled tobacco smoke were thought to be therapeutic. In 1571, a Spanish doctor named Nicolas Monardes wrote a history of medicinal plants of the new world, in which he claimed that tobacco could cure 36 health problems.² Cigarettes were developed for the treatment of asthma that were made of an anticholinergic substance and were available for purchase up until the 1970s (Elliott and

¹Mark Sanders runs a website highlighting the history of inhalational medicine at www.inhalatorium.com/page www. It contains many pictures of devices and so-called medications used by the inhalation route in the last 300 years, many of which now appear preposterous or even injurious.

²Boston University Medical Center. History of tobacco. <http://academic.udayton.edu/health/syllabi/tobacco/history.htm>. Accessed 30 June 2010.

Reid 1980). This chapter will focus on the administration of medications via inhalation during mechanical ventilation of infants and children.

The inhaled route for administering medications has significant advantages over other routes. These include (Le Brun et al. 2000):

- *Reduced first pass effect:* This term refers to reduction in the concentration of a drug before it reaches the systemic circulation. Once swallowed, a drug is absorbed by the digestive system. It passes through the liver before it reaches the systemic circulation. Often, most of the drug is metabolized in the liver, some to the point where only a small percentage of the ingested drug remains, reducing bioavailability.
- *Shorter lag time:* Since most aerosolized drugs are administered directly to the site of action when inhaled, there is generally reduced lag time between delivery and the start of the action of the drug. With bronchodilators this results in a nearly immediate effect.
- *Fewer systemic side effects:* Again, since the aerosolized drugs are typically administered directly to the site of action, there are typically fewer systemic side effects.

Some of the technical aspects, advantages, and limitations of creating and inhaling therapeutic aerosols in ventilated children are related to the anatomy of the pediatric airway and lung and the size of the equipment being used. By the 17th week of gestation, the full number of generations of conducting airways has been established (Wohl 2006). The implications of this are very important for the efficacy of inhaled medication in children. These airways are significantly narrower in diameter than in adults. The passage through and deposition of aerosols in these airways are substantially different than in adults. This is due, in part, to the fact that most aerosol-generating technology has been developed for use in adults. In addition, much of the performance data and conventional wisdom about the ability of various devices to deliver aerosols to

Table 30.1 Comparison of infant and adult lung and airway characteristics

Infant/adult	Infant	Adult
Trachea, diameter	4 cm	20 cm
Trachea, length	5–6 cm	10–12 cm
Tidal volume	20–40 mL	400–700 mL
Respiratory rate	30–40/min	12–14/min
Inspiratory flow rate	≤100 mL/s	500 mL/s

the middle and lower respiratory tract are predicated on the behavior of aerosols in the adult lung. Table 30.1 compares some basic structural and functional differences between the lungs of adults and infants.

Bronchodilators are the most commonly administered drug via the inhaled route in ventilated patients. For the purposes of analyzing the best way to give an aerosol, the following discussion will focus on the administration of inhaled bronchodilators. Many other drugs are available or under development in formulations that can be administered via the inhaled route, including antibacterials, antivirals, antifungals, immunosuppressive drugs, nonsteroidal anti-inflammatory drugs, surfactants, prostaglandins, mucolytics, antitussives, gene therapy vectors, insulin, heparin, ergotamine, calcitonin, human growth hormone, sildenafil, vaccines, morphine, and fentanyl (Rubin 2010). Often, the type of drug being aerosolized dictates the use of different kinds of aerosol-generating devices (Waldrep and Dhand 2008). Liposome encapsulation is emerging as a potentially better way to formulate drugs for aerosol deposition in the lungs. Liposomes are tiny vesicles or sacs that can be formed around solution to be inhaled. The liposomes create a more sustained response of the drug and fewer side effects (Dhand 2004). Newer formulations of drugs that are liposome encapsulated will require specific and sometimes different aerosol-generating technology (Waldrep et al. 1994; Saari et al. 1999; Zaru et al. 2007; Gagnadoux et al. 2008; Elhissi et al. 2007).

30.1.2 Characteristic and Behavior of Aerosols

An aerosol is a group of solid or liquid particles suspended in a gaseous medium. The aerosols generated by clinical devices are composed of many different sized particles and referred to as heterodisperse aerosols (or polydisperse). The distribution of particle sizes is an important characteristic that affects the ability of the aerosol to achieve therapeutic goals. One term used to describe distribution of the size of aerosol particles is *mass median aerodynamic diameter* (MMAD) which can be defined as the particle diameter that divides the distribution of particle sizes in half by mass. In other words, half of the mass of an aerosol is made of particles larger than the MMAD and half the mass is made up of smaller particles.

For a therapeutic aerosol like bronchodilator therapy to be effective, the particles must transit the aerosol-generating device, connecting tubing/device, and the upper airway, finally coming out of suspension and depositing on the walls of the medium and small airways. Therapeutic aerosols range in diameter from 0.1 to >10 μm . Particles >5 μm tend to deposit in the medium and larger airways, while particles <1.0 μm are so small as to be exhaled without depositing in the airway. For adults, aerosol generators are best that can produce particle size distributions with a high proportion of the particles in this respirable range (1–5 μm) (Heyder et al. 1986; Balášházy et al. 2007).

But these axioms about aerosol deposition by particle size in various parts of the airway are all based on the anatomy of the adult airway. It is not unreasonable to assume that the most efficacious distribution of particle sizes for infants and children is smaller than that postulated for adults, but I have never seen any literature that has analyzed or studied this issue.

When a suspended aerosol particle moves near enough to the walls of the airway, it comes

out of suspension and deposits. It is thought that this occurs at a distance from the wall of the airway of $\leq$ than one radius of the particle (Kleinstreuer et al. 2008). Mechanisms of this deposition include inertial impaction and gravitational sedimentation. Inertial impaction results when particles are moving in one direction in the gas stream through airways that are tortuous. The physical laws of motion govern the movement of these particles such that their inertia (or linear momentum) tends to carry them in one direction. The linear momentum of particles is the product of their mass times their velocity. Particles tend to continue in a straight line until acted on by another force or impacting the wall of the airway, where they deposit out of suspension. This effect will be more pronounced with larger particles because of their higher linear momentum, which explains why larger particles tend to deposit sooner, in the upper airways. Higher inspiratory gas flow rates should increase inertial impaction, again because particles moving at a higher rate have an increased linear momentum.

Gravitational sedimentation occurs when particles reside long enough in the airway to settle out and touch the walls of the airway when acted on by gravity. This is why breath holding can increase aerosol deposition in the airways, because during this pause in flow, the linear momentum of particles is lower and the effects of gravity can draw the particles into the walls of the airway. Lower flow rates can also enhance gravitational sedimentation, again because the suspended aerosol particles will have a lower linear momentum. This lower velocity of gas allows more transit time of the particles in the airway and more gravitational sedimentation is possible.

Aerosol characteristics are also affected by the phenomena of coalescence. When two aerosol particles come into relatively close proximity with one another, they combine to form a larger particle. Coalescence tends to happen when

particles come within a distance of one another less than 25 diameters of the particle sizes. Coalescence is increased during higher (more turbulent) flow rates because more turbulent flow will increase the number of particle collisions.

The combined effects of inertial impaction and coalescence (which creates larger particles from smaller ones) can cause increased relative amounts of an inhaled aerosol delivered to ventilated patients to deposit (1) on the walls of the tubing and chambers connecting the aerosol to the artificial airway, (2) in the artificial airway, and (3) in the larger and medium airways. Deposition profiles like this are generally not very therapeutic. As previously stated these phenomena are enhanced when inspiratory flow rates and respiratory rates are higher. They are also enhanced when both the artificial and natural airways are smaller. This makes delivery of inhaled aerosols to ventilated infants and small children very challenging, and many types of delivery systems result in very little of the total aerosolized dose actually getting through the equipment and the artificial airways to the parts of the patient lungs where the drug can be effective (Fink 2004). It is reported that pulmonary deposition of nebulized aerosols in neonates may be as low as 1 % of the nominal dose, compared to 8–22 % in adults (Rubin and Fink 2001).

There is emerging information that the nature of pulmonary disease affects the deposition of aerosols into different parts of the lung (Apiou-Sbirlea et al. 2010). This is because various degrees of airway constrictions, blockages, or remodeling cause disruption and redirection of flow into various parts of the lung. In part, this information has been developed using sophisticated mathematical modeling, and the overall complexity of the modeling makes straightforward application of this information at the bedside to improve aerosol delivery difficult. But in general, aerosol delivery will be improved by the application of pulmonary toilet procedures *before* aerosolized medications are administered

to patients in order to remove any blockages or narrowing of the airways related to retained secretions.

Many *in vitro* studies have been published, testing the delivery of aerosols during mechanical ventilation of infants and children (Rubin and Fink 2001; Cameron et al. 1991; Benson et al. 1991; Everard et al. 1992; Arnon et al. 1992; Grigg et al. 1992; Coleman et al. 1996; Garner et al. 1994, 2000, 2002; Lugo et al. 2001; Pelkonen et al. 1997; Wildhaber et al. 1998; Avent et al. 1999; Habib et al. 1999; Dubus et al. 2005). Generally, these studies use neonatal and pediatric lung models that compare the output of delivery devices like nebulizers and metered-dose inhalers (MDI) to the amount of the aerosol that can be recovered distal to the endotracheal tube. Fink published an excellent analysis of these studies (Fink 2004). For various types and brands of nebulizers, airway deposition of the emitted aerosol dose has been reported to range from 0.02 to 8.0 % with a mean of 2.01 ± 2.01 % ($\pm$ standard deviation). For MDIs deposition was reported from 0.12 to 15.5 %, with a mean of 4.70 ± 4.70 %. Figure 30.1 is derived from analysis of these studies and shows the distribution of drug delivery in these various lung models with nebulizers versus MDIs.

Consider the very large range and variation of device performance for both nebulizers and MDIs. Coefficients of variation for both distributions are 100 %. Variation notwithstanding, MDIs appear to be better devices than pneumatic nebulizers for delivering aerosolized medication during mechanical ventilation for reasons that will be described below.

Why such large variation and poor overall drug delivery in these studies? Because there are many factors that affect the efficacy of inhaled drug delivery systems during mechanical ventilation in pediatric patients. These include (1) the type of aerosol generator used, (2) the location or placement of the aerosol generator in the ventilator circuit, (3) the use of humidified gas, and (4) the patients' ventilatory parameters.

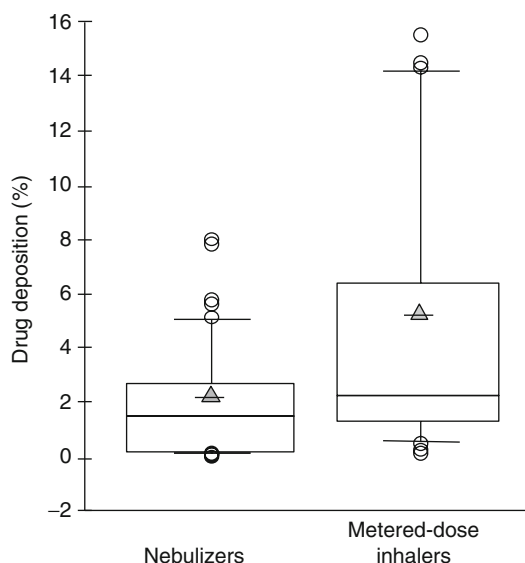


Fig. 30.1 Distribution of summarized results from 13 published in vitro studies of drug deposition in various neonatal and pediatric lung models during mechanical ventilation comparing the performance of nebulizers and metered-dose inhalers. *Box plots* represent the percent drug deposition reported in each study. Some studies reported several deposition rates because they tested various devices and/or delivery configurations. *Circles* represent aerosol particles of various sizes. *Shaded triangles* represent the arithmetic mean (Adapted from the work of Fink (2004))

30.1.3 Factors Affecting Aerosol Delivery During Mechanical Ventilation

30.1.3.1 Types of Aerosol Generators Used

There many different types and brands of aerosol-generating devices. The overwhelming majority of all inhaled medications during mechanical ventilation are delivered using either nebulizers or MDIs, but at one time, the majority of medication delivery during mechanical ventilation of infants in the USA was done with pneumatic nebulizers, (Salyer and Chatburn 1990) but practice is evolving and MDI's use is increasing (Ballard et al. 2002).

Nebulizers can be broadly categorized into two types: (1) pneumatic nebulizers and (2)

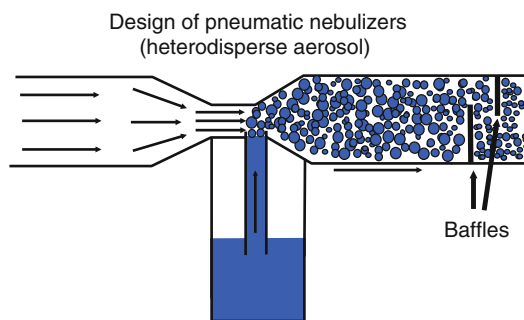


Fig. 30.2 Conceptual schematic representation of a typical pneumatic nebulizer. Circles represent aerosol particles of various sizes. Note the position of the baffles. The distribution of particle sizes is greatly improved as the aerosol passes through the baffles where many larger particles impact the baffles and deposit. The design of the nebulizers is such that the aerosol that deposits on the baffles drains back into the nebulizer fluid chamber and is re-nebulized

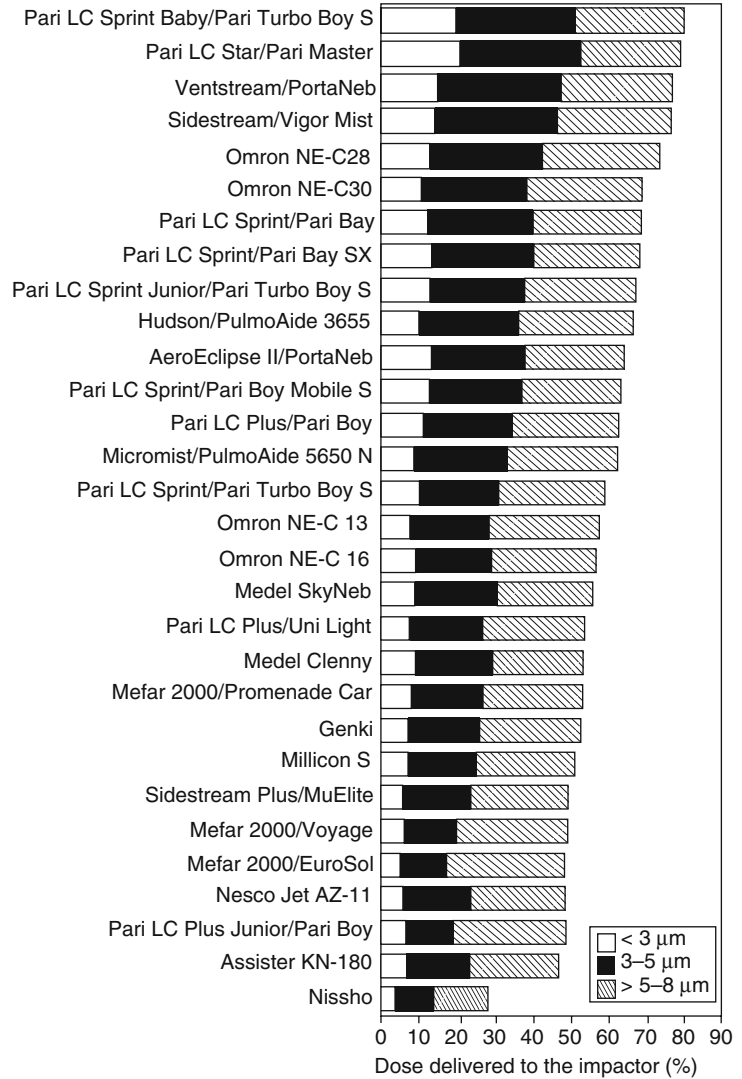
vibrating mesh nebulizers.³ For use during mechanical ventilation, MDIs are generally used in one of three ways: (1) with an in-line adapter, (2) with a spacer, and (3) with a valved holding chamber.

30.1.3.2 Pneumatic Nebulizers

Pneumatic (or jet) nebulizers employ the Venturi effect to create an aerosol. When a gas stream is directed from a wider to a narrower orifice tube, the velocity of the gas increases, and its pressure drops. If the size of the narrowing is properly calibrated, a capillary tube connected to a fluid reservoir can be inserted in the narrowed orifice and fluid will be drawn into the gas stream by this reduced pressure and broken into suspended particles (an aerosol). Figure 30.2 is a conceptual schematic representation of the design of pneumatic nebulizers. The Venturi effect typically creates a heterodisperse aerosol that has very

³ A third type, the ultrasonic nebulizer produces aerosols by converting electrical energy into high-frequency (ultrasonic) vibration of a plate located in a fluid bath. This conversion produces heat, and ultrasonic devices tend to warm the medication, which in some cases is not a good idea. They are not widely used for mechanically ventilated patients, and for the sake of brevity, they will not be included in this discussion.

Fig. 30.3 Droplet size distribution of budesonide inhalation suspension up to 8 μm in various brands of pneumatic nebulizers. Three units of each brand were tested. The results are expressed as a percentage of budesonide mass delivered to the impactor (Used with permission from Berg and Picard (2009))



high variation in particle sizes and limited proportion of particles in a range suitable for deposition in the lungs. This is remedied by the use of baffles in the nebulizer which are designed so that larger particles will impact on the baffles and recovered in the nebulizer for re-nebulization, leaving the remaining aerosol composed of a higher proportion of aerosol particles in the respirable range.⁴

Not all pneumatic nebulizers are created equal, although this reality is not yet fully appreciated by many clinicians. Considerable perfor-

mance variation has been reported between *brands* of the same types of nebulizers in the past (Alvine et al. 1992; Hess et al. 1996) and more recently (Berg and Picard 2009). This variation takes the form of differences in the aerosol characteristics, such as the respirable range of particles created by these nebulizers. Additionally, there is almost certainly variation in performance within the *same* brands/models of nebulizer owing to imprecision in the manufacturing process, although I am unaware of any significant work published that quantifies this variation. Figure 30.3 describes variation between brands of pneumatic nebulizers in the distribution of particle sizes.

⁴Respirable range describes aerosol particle sizes in the 1–5 μm range.

Variable nebulizer performance and application may help to explain some of the lack of response to bronchodilators so often seen during treatment of ventilated patients. In many cases, it may be that the patient is getting very little of the aerosolized medication delivered to the airways. It can also explain the wide variation and generally poor findings reported in the literature for various studies of delivery and/or deposition of aerosolized medications.

30.1.3.3 Vibrating Mesh Nebulizers

Vibrating mesh (or plate) nebulizers employ a small plate containing $\approx 1,000$ very small cone-shaped holes through which a liquid is forced by vibrating the plate at very high frequencies over a thin layer of liquid. As the liquid is forced through the holes in the vibrating plate, it is aerosolized. These nebulizers demonstrate increased efficiency of drug delivery to the respiratory tract compared to some pneumatic jet nebulizers (Dubus et al. 2005; Dhand 2002; Skaria and Smaldone 2010; Ari et al. 2010a, b). However, there are different design approaches between brands of these types of nebulizers (Ari et al. 2009), and as with pneumatic nebulizers, there are most probably significant performance differences between brands.

Vibrating mesh nebulizers also have the added advantage of not generating any additional flow, which pneumatic nebulizers do. This is important if the nebulizer is placed in-line in the circuit of some types of ventilators. Many of the latest generation of critical care ventilators measure flow going into and out of the ventilator circuit. These flow measurements are used in feedback loops by the ventilator for, among other things, disconnection alarm management. When a pneumatic nebulizer is placed in-line, the flow used to operate the nebulizer is added into the ventilator circuit, which can potentially affect efficiency of some alarms and the accuracy of some flow measurements. In some older models of ventilators, this added flow can inadvertently increase tidal volume by relatively large amounts when very low tidal volume settings are used (Salzer et al. 1990).

One disadvantage of the vibrating mesh nebulizers is that they are more costly than the typical disposable pneumatic nebulizer or MDI with spacer/holding chamber. However, such costs can

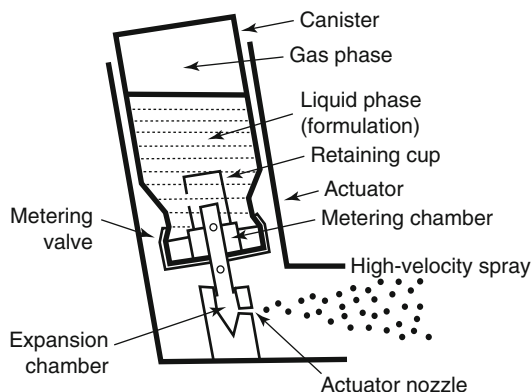


Fig. 30.4 Schematic diagram of metered-dose inhaler (Used with permission from Newman (2005))

be easily justified when viewed in the light of the overall cost of being on a ventilator and in an intensive care unit. The use of more effective aerosol-generating technology might well shorten length ventilation and thus length of stay in the intensive care unit, although this has yet to be proven.

30.1.3.4 Metered-Dose Inhalers

Metered-dose inhalers are small canisters filled with a pressurized propellant and medication. When the MDI is actuated, the propellant and medication mix and are rapidly expelled from the MDI in a plume of aerosol (Fig. 30.4) (Newman 2005). The velocity of this plume of aerosol-laden gas makes the successful use of MDIs very technique dependent. The actuation of the MDI needs to be synchronized with the inspiratory cycle. If the output of an MDI is pointed directly into the mouth, much of the aerosol will be deposited in the mouth and pharynx because the high initial velocity of the plume causes inertial impaction of particles in the mouth. This phenomenon also occurs if the MDI is actuated directly into a ventilator circuit by use of certain types of adapters, with much of the drug being lost in the circuit and the connectors.

One way to overcome this is the use of certain types of adapters, spacers, or holding chambers to improve the interface of the MDI with the patient's ventilator circuit/airway. Types of adapters include elbow adapters, unidirectional or bidirectional in-line adapters, spacers, and holding chambers. The elbow adapters typically connect to the ETT, whereas the in-line adapters,

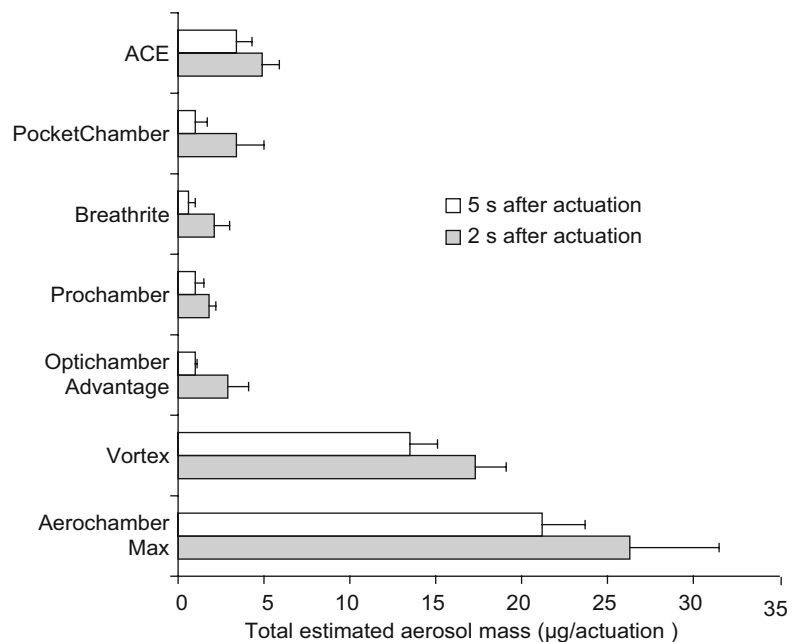
spacers, and chamber adapters may be placed in the inspiratory limb of the ventilator circuit or connected directly to the artificial airway.

The MDI spacer is a quasi-cylindrical reservoir that holds several 100 mm of gas. The MDI plume mixes with the gas in the spacer and slows the velocity of the plum while the aerosol remains suspended so it can be inhaled. This significantly reduces inertial impaction.

A holding chamber is a spacer that is designed with valves in such a fashion to separate inspiratory and expiratory flow. This valved configuration allows infants and children to be given several subsequent breaths while connected to the holding chamber, thereby increasing the likelihood that more of the emitted dose of the MDI will be deposited in the lungs. These were developed in part because of concerns that the spacer could act as mechanical dead space if the patient was allowed to exhale into the spacer and rebreathe the gas in the spacer. However, it has been shown in laboratory modeling that very little CO₂ is rebreathed during drug administration using an MDI with spacer (Lugo et al. 2000). Nevertheless, some clinicians still feel that limiting the time the spacer is in the circuit is necessary to avoid CO₂ rebreathing, but this technique has been shown to reduce the amount of drug delivered to the patient (Lugo and Ballard 2004).

But not all spacers and valved holding chambers are created equal either. Most brands of MDI spacers or holding chambers are manufactured from materials that acquire an electrostatic charge on the inner surface. This charge tends to attract suspended aerosol particles which deposit on the inner walls of the spacer, significantly reducing bioavailability of the drug (Wildhaber et al. 1996). This effect can be diminished by rinsing the inside of the chamber with soap and water. However, this is not as effective as using spacers and holding chambers made from non-electrostatic materials, which allow for a significantly larger portion of the emitted dose to exit the spacer (Rau et al. 2006; Nair et al. 2009). Figure 30.5 illustrates differences in the amount of emitted dose from an MDI that is used with holding chambers that were made from electrostatic versus non-electrostatic materials. The PARI Vortex (PARI Inc) and AeroChamber MAX (Monaghan Medical) products were both made of non-electrostatic materials. The use of a spacer/holding chamber with the MDI during mechanical ventilation results in a four to six-fold increase in drug delivery when compared with an elbow adapter or unidirectional in-line adapter (Dhand 2005; Bishop et al. 1990; Rau et al. 1992; Fuller et al. 1994; Diot et al. 1995). While MDIs are better than pneumatic nebulizers at delivering

Fig. 30.5 Results of a study of the effect of using non-electrostatic material to construct spacers and holding chambers. Displayed from several brands of spacers. The Vortex and AeroChamber products are both constructed of non-electrostatic materials. This effect was scene both before and after rinsing of the chambers (Adapted from Rau et al. (2006))



inhaled medication to ventilated patients, (Hess 2002; Dhand and Guntur 2008; Lugo et al. 2001) this is only true if the devices are used with the appropriate interface with the ventilator circuit.

Conventional wisdom in the recent past suggested that MDIs with spacers or valved holding chambers were more expensive than disposable pneumatic nebulizers. We demonstrated that when sophisticated costing models were used that analyzed the total cost of aerosolized medication administration, including labor, MDIs with valved holding chambers were less costly than pneumatic nebulizers in a pediatric population (Salyer et al. 2008).

30.1.3.5 Location of the Aerosol Generator

Figure 30.6 illustrates various options for location of an aerosol-generating device in a ventilator circuit. Device location has been demonstrated to have a large effect on drug delivery. In a series of well-designed experiments, Ari and colleagues (Ari et al. 2010b) have described the effects of location, nebulizer type, humidification, and bias

flow. Figure 30.7 illustrates some of the results of their work. They demonstrated that by variously combining these factors, drug delivery past the endotracheal tube could be increased from 2.5 to 30 % of the emitted dose. Generally, the optimum location is dependent on the type of aerosol-generating device. For MDIs with spacer, the best location was between the ventilator circuit and endotracheal tube. For pneumatic (jet) nebulizers, the optimal location appears to be in the inspiratory limb of the ventilator circuit, a short distance ($\cong 15$ cm) from the Y-piece. For vibrating mesh nebulizers, the optimal location was also in the inspiratory limb of the circuit.

Another option is to ventilate the patient with a manual resuscitator that is connected to the MDI-holding chamber assembly which in turn is connected to the ventilator. However, it has repeatedly shown that ventilation can be highly variable during neonatal or pediatric manual ventilation and that this variability is dependent in part on the type of resuscitator used (Salyer 2009). Thus, manual ventilation introduces more potential variation into a procedure that already

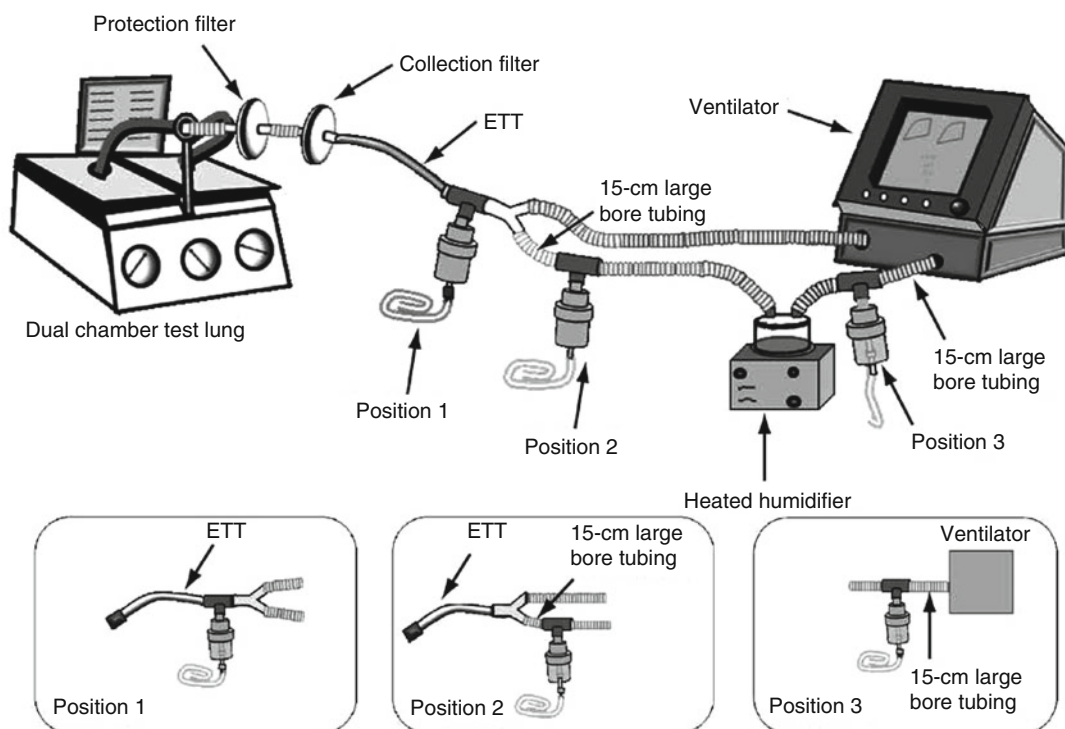
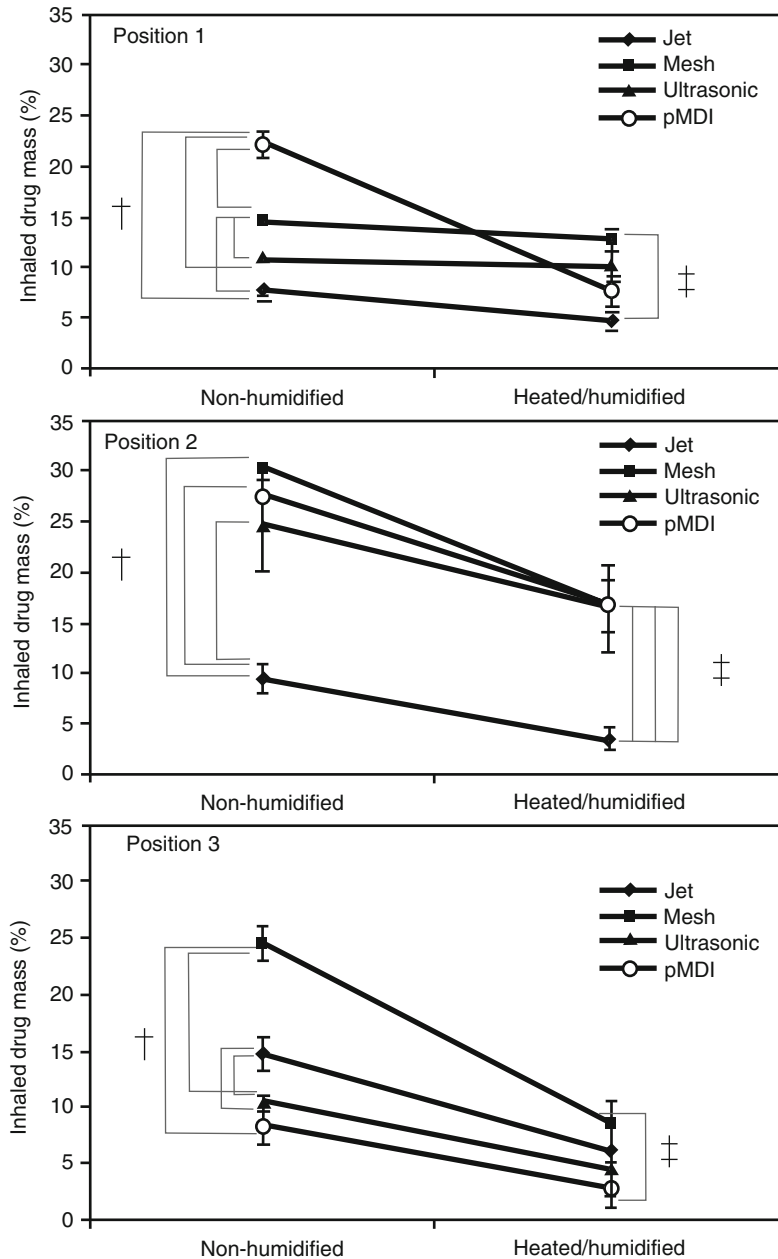


Fig. 30.6 Schematic representation of typical options for placing aerosol-generating devices in the ventilator circuit during mechanical ventilation, including dual-chamber test

lung, filters, endotracheal tube, and ventilator circuit, with and without heated wires. Three aerosol generator positions are shown (Used with permission from Ari et al. (2010b))

Fig. 30.7 Results of a study of the effects of type and location of aerosol generator as well as humidity on drug delivery during mechanical ventilation. Positions 1, 2, and 3 are described in Fig. 30.6. Statistical significance is denoted by †, and ‡ (Used with permission from Ari et al. (2010b))



demonstrates high variability in efficacy and is probably not generally recommended.

30.1.3.6 Humidification of Inhaled Gas

It has been known for some time that the aerosolized drug delivery is adversely affected by the humidification of the carrier gas (Lange and Finlay 2000; Fink et al. 1999; Miller et al. 2003). Ari and her colleagues added to this understanding, showing that humidified carrier gas reduces the efficacy of aerosol delivery and that this effect

is more pronounced the longer the aerosol resides in the humidified gas stream for nebulizers. This phenomenon occurs because some types of aerosol particles are hydrophilic, which means that in the presences of higher relative humidity, water comes out of vapor phase and attaches to the outside of the particle, increasing its size. Thus there are a higher proportion of larger particles and more inertial impaction of aerosol particles in parts of the delivery system and airways where they cannot be therapeutic. (Balášházy et al. 2007)

30.1.3.7 Ventilator Settings

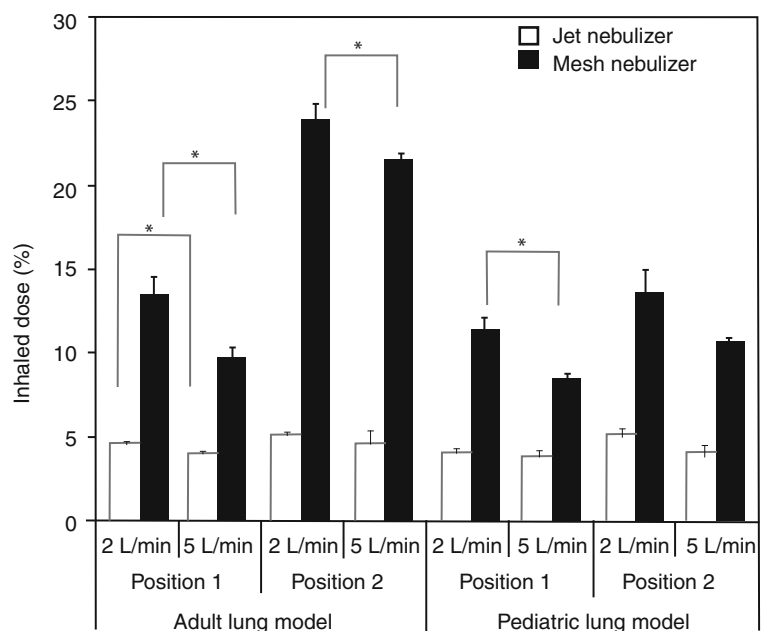
Theoretically, higher flow rates should result in more turbulent movement of gas through the airways. Through the phenomena of coalescence, at higher flow rates there will be more collisions of aerosol particles, resulting in the formation of larger particles. Loss of aerosol through inertial impaction will also be increased as flow rates increase because particles will have more linear momentum as they move through the tortuous path of the airways. And larger tidal volumes should also enhance drug delivery due to increased dilation of the airways during the positive pressure phase of the inspiratory cycle. An inspiratory pause ought to be efficacious as it should allow for more deposition from gravitational sedimentation.

However, research findings on the effect of ventilator settings are divergent. Ari et al. demonstrated in adult and pediatric lung models that increasing bias flow decreases drug delivery (see Fig. 30.8) (Ari et al. 2010a). Others have demonstrated that increasing tidal volume, lowering flow rates, lengthening inspiratory times, and synchronizing devices with the patients' inspiratory effort improve drug delivery (Fink et al. 1996, 1999; O'Riordan et al. 1992; Dolovich 2000; Dhand 2008). Again, most of this work has been done using in vitro lung models.

But Mouloudi et al. were unable to detect any difference in the clinical response to inhaled bronchodilators delivered via MDI with spacer to ventilated patients when flow rates were decreased nor when flow patterns were altered from decelerating to continuous inspiratory flow profiles nor when an inspiratory pause was introduced nor when tidal volume was increased by 4 ml/kg (Mouloudi et al. 1998, 1999; 2000; Malliotakis et al. 2007). Garner and colleagues used a neonatal ventilation model to show that albuterol delivery was not different in any of the three different modes and when large increases in spontaneous respiratory rate were introduced (Garner et al. 2002). The divergence of findings in the effect of ventilator settings on drug delivery might well be related to the wide variety of aerosol-generating devices tested and a lack of standardized device location and use of humidification.

This divergence notwithstanding, the majority of the published literature is in support of the idea that aerosolized drug delivery is indeed affected by alterations in the ventilator settings as described above. It seems prudent and reasonable to try to optimize drug delivery by using ventilator settings that serve the dual purpose of meeting the patients' physiologic demands and improve the amount of drug delivery. Especially since delivery of aerosolized drugs is so inefficient, even under optimal conditions.

Fig. 30.8 The effect of increasing the bias flow on the delivery of aerosolized medications past the tip of the endotracheal tube in an adult and pediatric lung model. Position 1 is in the inspiratory limb ≈ 15 cm from the Y-piece, while position 2 is in between the outlet of the ventilator and the heated humidifier which was operated at 35 °C. Adult $V_T = 500$ mL, pediatric $V_T = 100$ mL (Used with permission from Ari et al. (2010a)). Asterisk denotes statistical significance



30.2 Specific Inhalational Treatment

30.2.1 Bronchodilator Therapy

John Salyer

30.2.1.1 Efficacy and Utilization of Inhaled Bronchodilators

It has been suggested by some that there is little evidence that bronchodilator therapy has any influence on patient outcomes related to pulmonary disease during mechanical ventilation (Dhand 2007; Chang et al. 2007). The mostly widely used inhaled bronchodilators during mechanical ventilation are β_2 agonists like albuterol (salbutamol). My observations indicate that the drug is overutilized in ventilated patients and this has also been reported in the literature (Dhand 2008). Chang and colleagues reported that 36 % mechanically ventilated patients who do *not have clinical evidence of obstructive lung disease* received inhaled bronchodilators during their ventilator course (Chang et al. 2007). I have also observed that many patients do not appear to have any “apparent” response to the medication. Although the most common clinical goal for aerosolized β_2 agonists during mechanical ventilation is relief of bronchospasm, other indications for this drug and route have been reported.

Benefits of inhaled β_2 agonists in mechanically ventilated patients have been reported to include:

- *Relief of bronchospasm:* Airway resistance (R_{aw}) will decrease as bronchospasm is relieved in ventilated patients. Technically, the measurement of R_{aw} (and lung compliance) requires the insertion of an esophageal balloon to facilitate measurement of esophageal pressure which is used as a surrogate for intrapleural pressure. Since this is rarely done in most clinical scenarios, resistance of the total respiratory system (R_{RS}) is used as a surrogate. This value is typically displayed as cmH₂O/L/s and is calculated by most

contemporary critical care ventilators. Owing to imprecision and normal variability of these types of biological measurements, a decrease of >15 % is usually required to be confident there has been a response to bronchodilators (Torres et al. 1997). And care should be taken to look at this displayed value on the ventilator for several breaths to make sure there is reproducibility, since erratic spontaneous breathing patterns and ventilator dyssynchrony are prevalent in infants (Mouloudi et al. 1998; Paetow et al. 1999; Kapasi et al. 2001). If the ventilator used does not calculate resistance, peak airway pressure decreases can be a surrogate for response to bronchodilators, but only if the patient is in a volume-controlled, decelerating flow mode of ventilation. Obviously, peak airway pressure will remain constant in pressure-controlled modes. And there can be other causes for decreasing airway pressures including removal of retained secretions. This is another reason why it is a good idea to do pulmonary toilet before you give an inhaled bronchodilator. Another way to evaluate response to bronchodilators is to evaluate the appearance of the flow volume loops. Holt and colleagues illustrated this in Fig. 30.9 (Holt et al. 1995). Compliance of the respiratory system (C_{RS}) has also been shown to improve significantly after bronchodilator administration in ventilated infants (Rotschild et al. 1989; Denjean et al. 1992; Sivakumar et al. 1999). Again, changes of >15 % is necessary to have confidence of a real clinical response.

- *Improved mucociliary clearance:* Mucociliary clearance has been reported to be profoundly diminished in patients who require mechanical ventilation (Konrad et al. 1994, 1995; Dolovich et al. 1998). Inhaled β_2 agonists have been shown to improve mucociliary clearance (Bennett 2002; Houtmeyers et al. 1999; Foster et al. 1976; Gatto 1993). The effect seems to be more enhanced at higher

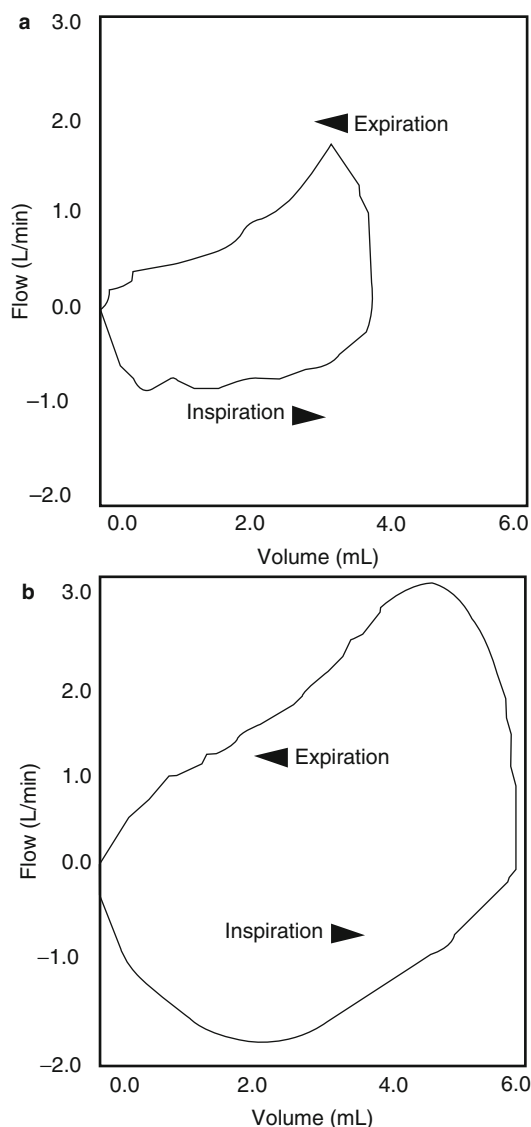


Fig. 30.9 Flow volume loops during mechanical breaths of an infant who had a positive response to aerosolized bronchodilators. (a) Before treatment and (b) 20 min after treatment during mechanical breaths (Used with permission from Holt et al. (1995))

doses and for prolonged therapy (Dolovich 2000). This improvement in mucous transport is caused by an increase in mucociliary beat frequency. However, a link between increased ciliary beat frequency and improved

pulmonary outcomes in patients receiving mechanical ventilation has not yet been established, though some investigators have tried and failed to find an effect on outcomes (O’Riordan et al. 2006).

- *Treatment of hyperkalemia:* Elevated serum levels of potassium are a common complication of intensive care (Buckley et al. 2010). Inhaled β_2 agonists are known to induce hypokalemia (Burgess et al. 1989; Allon and Copkney 1990; Habashy et al. 2003; Hung et al. 1999). In one study of ventilated neonates receiving inhaled albuterol, 28–36 % of these very low-birth-weight infants developed hypokalemia (Mhanna et al. 2009). This effect appears to be prevalent only after many repeated doses since clinically significant reductions in serum potassium levels were not seen when six doses of inhaled β_2 agonists were given over a period of 3 h in one study of pediatric asthma patients (Kaashmiri et al. 2010).
- *Improvement in pulmonary mechanics:* As stated above, inhaled β_2 agonists have been shown to reduce R_{RS} C_{RS} in ventilated children. In addition, inhaled β_2 agonists have been reported to (1) reduce plateau pressures and reduce airflow resistance in ARDS, (Wright et al. 1994); (Gay et al. 1987) (2) lower intrinsic PEEP (Morina et al. 1997), (3) and decrease work of breathing (Mancebo et al. 1991).

It is widely held among respiratory therapists that inhaled bronchodilators in ventilated patients are overutilized, which is probably true, but there is no published literature on this subject. In general, the utilization of respiratory therapy procedures is almost always reduced when standardized clinical protocols are introduced. There is no reason to presume that the utilization of inhaled bronchodilators to mechanically ventilated infants and children would not also benefit from protocol standardization that would result from the use of systematic protocols (Stoller 2001).

30.2.2 Inhaled Selective Pulmonary Vasodilators

Peter Dahlem

Educational Aims

To understand that:

- Hypoxemia in ALI is caused by ventilation/perfusion mismatch.
- Pulmonary perfusion is disturbed by disbalance in alveolar perfusion.
- Redistribution of blood flow to ventilated areas can improve oxygenation.

Acute hypoxic respiratory failure in clinical conditions such as acute lung injury (ALI) is characterized by severe hypoxemia due to indirect or direct lung injury (Bernard et al. 1994). The severity of hypoxemia is associated with mortality and determines long-term sequelae (Dahlem et al. 2007; Rubenfeld et al. 2005; Randolph 2009). Mechanical ventilation (MV) with high concentrations of oxygen in the inspired gas ensures ventilation and improves oxygenation. MV itself and oxygen are however potential harmful measures (The Acute Respiratory Distress Syndrome Network 2000). Therefore, other therapies which improve oxygenation may contribute to a better outcome.

It is important to know that hypoxia in these situations is caused by ventilation/perfusion mismatch, intrapulmonary shunting, and imbalanced pulmonary blood flow. Therefore, carrying drugs to the alveolar capillary unit with the potential to normalize pulmonary blood flow would be a therapeutic clue. It has been shown that systemic administration of vasodilating drugs not only lowers pulmonary vascular resistance but also decreases systemic vascular resistance. As a consequence intrapulmonary shunting and hypoxemia increase (Radermacher et al. 1989; Rossaint et al. 1993). With the concept of selective pulmonary vasodilatation, drugs are delivered to the pulmonary vascular bed directly by the inhalative route, avoiding the systemic side effects. Until now, inhaled nitric oxide (INO) and aerosolized

prostaglandins (PGI₂, PGE₁, iloprost) are the most commonly studied drugs for this indication (Dahlem et al. 2007). They all lower pulmonary vascular resistance, redistribute blood flow to ventilated areas, do not affect systemic circulation, and may have anti-inflammatory effects additionally.

Pharmacologically, prostacyclins increase of 3',5'-cyclic adenosine monophosphate in vascular cells, leading to relaxation of smooth muscle cells. They act immediate with short half-life times between 2 and 10 min for the natural prostacyclins, PGI₂ and PGE₁, and about 30 min for the synthetic iloprost (Vane and Botting 1995; Hoeper et al. 2000). Delivery of aerosols is easily and accomplished by ultrasonic nebulizers which are integrated in the respiratory circuit (Walrmath et al. 1993; Harvey et al. 1997).

INO induces formation of 3',5'-cyclic guanosine monophosphate, causing relaxation of vascular smooth muscle cells and vasodilatation of blood vessels (Palmer et al. 1987; Moncada 1992). INO gas is mixed to the inspired gas of the ventilator. Due to its importance in many pathways and therapeutic properties and applications, NO was announced the molecule of the year in 1992 by *Science*.

Both drugs have been shown in uncontrolled case series to lower pulmonary vascular resistance and to improve oxygenation. In a systemic review and meta-analysis of 12 randomized controlled trials (RCTs) in adult patients with ALI, INO improved oxygenation, but did not improve overall outcome such as mortality. It was suggested that it also may induce renal failure as a drug-related complication (Adhikari et al. 2007). In acute hypoxic respiratory failure in adults and children, a recently completed systemic review of INO by the *Cochrane Collaboration* concluded similarly that INO improves oxygenation for a short period of 24–96 h but did not affect relevant outcome parameters such as mortality. It was not recommended for routine use but only for rescue treatment (Afshari et al. 2010).

There is only one RCT yet published investigating the benefits of inhaled PGI₂ in ALI (Dahlem et al. 2004). In 14 children PGI₂ improved the oxygenation index (fraction of

inspired oxygen $\times$ mean airway pressure/partial arterial oxygen tension) by 26 % with an optimal dosage of 30 ng/kg/min during a 20 min study period. Relevant outcome data such as mortality have not been examined. A recently completed systematic review by the *Cochrane Collaboration* concluded that beside this single RCT, no relevant data are available (Afshari et al. 2010). Therefore, inhaled prostaglandins should not be recommended for routine use (personal communication, Cochrane review in press). Two new trials with aerosolized prostaglandins are currently under way.

To summarize, drugs used for selective pulmonary vasodilatation have shown to improve oxygenation but not overall outcome of patients with ALI/ARDS. Therefore, these concepts need further attention not only for rescue situations but also for further well-designed trials with large numbers of patients. Furthermore, together with other measures such as protective mechanical ventilation, prone positioning, surfactant therapy, and HFOV, it has the potential to contribute to better outcome in children with acute hypoxic failure/ALI/ARDS.

In the future, other drugs (e.g., sildenafil, agonists of soluble guanylate cyclase) which have shown to lower pulmonary vascular resistance in experimental studies might initiate clinical trials for these indications (Ichinose et al. 2001; Evgenov et al. 2007).

Essentials to Remember

- Selective pulmonary vasodilation can redistribute blood flow to ventilated areas.
- Improved pulmonary blood flow can improve oxygenation.
- The concept of selective pulmonary vasodilation does not affect overall outcome.
- The concept of selective pulmonary vasodilation may be an adjunct to mechanical ventilation within the context of additional therapies.

30.2.3 Inhaled Antibiotic Therapy

Ari Joffe

Educational Goals

- To review the data on efficacy of aerosolized antibiotics for prevention of ventilator associated pneumonia.
- To review the data on efficacy of aerosolized antibiotics for treatment of ventilator associated pneumonia.

30.2.3.1 Why Consider Aerosolized Antibiotic Therapy?

Aerosolized antibiotics are theoretically attractive for prevention and treatment of ventilator-associated pneumonia (VAP). Potential advantages of aerosolized antibiotics include achieving high drug concentrations at the site of infection in the lung, avoiding toxicity of antibiotics that are given systemically, and achieving this high concentration of potentially systemically toxic antibiotics effective against multidrug-resistant bacteria (Wood and Swanson 2007). In the prevention of VAP, strategies that prevent airway colonization such as semi-recumbent positioning and subglottic suctioning endotracheal tubes have been found effective, suggesting aerosolized antibiotics may also prevent this early stage in the pathophysiology of VAP (MacIntyre and Rubin 2007). In patients with cystic fibrosis, aerosolized antibiotics can prevent exacerbations and hospitalizations and may also be therapeutic in early *Pseudomonas aeruginosa* lung infections. In addition, aerosolized pentamidine has been effective at prevention of *Pneumocystis jirovecii* pneumonia.

Despite these theoretical advantages, the data to date do not yet support widespread use of aerosolized antibiotics in ventilated patients. Potential reasons for concern include whether the topical antibiotic in the airways has adequate lung penetration to fight deep-seated infection like pneumonia and possible adverse effects including bronchospasm. In addition,

aerosol delivery can involve changing ventilator settings and has the small risk of introducing infection. Finally, there is great concern regarding development of bacterial resistance with widespread use of aerosolized antibiotics (MacIntyre and Rubin 2007; Wood and Swanson 2007).

30.2.3.2 Aerosolized Antibiotics for the Prevention of Ventilator-Associated Pneumonia

Early trials of aerosolized antibiotics to prevent VAP showed a lack of efficacy, and some showed increased development of resistant bacteria (Wood and Swanson 2007). More recent trials selected patients at higher risk for VAP given shorter durations of prophylaxis, and had more promising results in prevention of VAP (Wood and Swanson 2007). A meta-analysis from 1950 to 2005 found only eight comparative trials, of which only five were randomized controlled trials (RCT), studying antibiotics given via the respiratory tract for the prevention of ICU-acquired pneumonia (Falagas et al. 2006). Only one RCT of high quality studied the use of aerosolized antibiotics; the other RCTs studied endotracheal instillation of antibiotics (two trials) or were of low quality (two trials). Various antibiotics were used, including gentamicin, polymyxins, colistin, tobramycin, and ceftazidime. The meta-analysis found a reduction in ICU-acquired pneumonia (OR 0.49; 95 % CI 0.32–0.76) without any difference in mortality (OR 0.86; 95 % CI 0.55–1.32). There were insufficient data to allow a meaningful synthesis of evidence regarding emergence of resistance, and no study looked systematically at emergence of resistance (Falagas et al. 2006). It is possible that the aerosolized antibiotics could suppress microbial growth and lead to reduction in the *diagnosis* of VAP. In view of the limited study (a total of 167 patients in the three RCTs examining aerosolized antibiotics), significant concern over development of bacterial

resistance particularly with widespread use, and confusion about what drug, dose, frequency, and duration of antibiotic to use, most organizations have recommended against routine use of aerosolized antibiotics for prevention of VAP (ATS 2005; CDC 2004; Muscedere et al. 2008b; Rotstein et al. 2008).

30.2.3.3 Aerosolized antibiotics for the treatment of VAP

A meta-analysis from 1950 to April 2007 found only 5 RCTs representing a total of 176 patients with pneumonia where antibiotics given via the respiratory tract were used for treatment of nosocomial pneumonia (Ioannidou et al. 2007). Only two RCTs (including 61 patients) used an aerosolized antibiotic; the other three used antibiotic instilled via the endotracheal tube. Concurrent systemic antibiotics were permitted in 4 of the trials. All the trials were of low or moderate quality. In intention to treat analysis of the 4 trials, there was better treatment success (OR 2.75; 95 % CI 1.29–4.44), defined as the clinical, laboratory, and radiologic improvement of the patients according to the authors of each trial. There was no difference in mortality, microbiological success, or toxicity (Ioannidou et al. 2007). This meta-analysis suggests that aerosolized antibiotics for treatment of VAP should be studied in large well-conducted RCTs before routine use could be considered. Most organizations have recommended against routine use of aerosolized antibiotics for treatment of VAP (ATS 2005; Muscedere et al. 2008a; Rotstein et al. 2008).

Some small case series have reported encouraging responses when aerosolized antibiotics, usually an aminoglycoside or colistin, were added to systemic antibiotics in previously nonresponding patients (Linden and Paterson 2006; Pereira et al. 2007; Wood and Swanson 2007). It may be reasonable to consider adding an aerosolized antibiotic to systemic treatment in patients with multidrug-resistant gram-negative organisms that are not responding to therapy (ATS 2005). This could

be considered salvage therapy, although the usefulness of this approach is unknown.

30.2.3.4 Considerations in Aerosolizing Antibiotics in Ventilated Patients

Earlier in this chapter, general issues of drug nebulization during mechanical ventilation were considered. It is likely that with antibiotics, it is best to use normal saline as the diluent and to completely fill the nebulizer reservoir (Wood and Swanson 2007). A nebulizer that produces a mean droplet size of 1–5 μm has the best chance to deposit drug in the distal airways (Wood and Swanson 2007). Antibiotics that have been used in limited study include gentamicin, tobramycin, colistin, ceftazidime, and polymyxin B (Falagas et al. 2006; Ioannidou et al. 2007; Pereira et al. 2007; Wood and Swanson 2007). Imipenem does not aerosolize well and should not be used (Wood and Swanson 2007). With tobramycin, a preservative-free formulation used in cystic fibrosis may minimize adverse reactions (Wood and Swanson 2007). Pretreatment with salbutamol may improve tolerability based on data using aerosolized pentamidine (Wood and Swanson 2007).

Unfortunately, based on the current studies, if an aerosolized antibiotic is used, it is unclear what dose should be used, when the medication should be started, what frequency to use, and the what duration to use (MacIntyre and Rubin 2007). The dosage used in adults in the published studies has been variable.

30.2.3.5 Recommendations for Using Aerosolized Antibiotics in Ventilated Children

The data reviewed above suggests that aerosolized antibiotics for prevention or treatment of VAP cannot be recommended at this time, outside of a randomized controlled trial. The data to support aerosolized antibiotics in preventing or treating VAP are weak, and there is a significant concern regarding emergence of antibiotic

resistance. It may be reasonable to consider adding an aerosolized antibiotic to systemic treatment as salvage therapy in a patient with multidrug-resistant gram-negative organisms that is not responding to therapy (ATS 2005). What antibiotic to use and at what dose is not known. It is likely that inhaled tobramycin at doses used in children with cystic fibrosis would be the first choice if antibiotic sensitivity results are compatible. A second choice would be inhaled colistin, polymyxin B, or ceftazidime at doses used in adults based on mg/kg (Falagas et al. 2006; Ioannidou et al. 2007; Wood and Swanson 2007). It should be emphasized that this would be salvage therapy, is not recommended for routine use, and the efficacy of this approach is unknown.

Essentials to Remember

- The data reviewed suggests that aerosolized antibiotics for prevention or treatment of VAP cannot be recommended at this time, outside of a randomized controlled trial. The data to support aerosolized antibiotics in preventing or treating VAP are weak, and there is a significant concern regarding emergence of antibiotic resistance.
- It may be reasonable to consider adding an aerosolized antibiotic to systemic treatment as salvage therapy in a patient with multi-drug resistant gram negative organisms that is not responding to therapy. What antibiotic to use, at what dose, and the efficacy of this approach is not known. It is likely that inhaled tobramycin at doses used in children with cystic fibrosis would be the first choice if antibiotic sensitivity results are compatible. A second choice would be inhaled colistin, polymyxin B, or ceftazidime at doses used in adults based on mg/kg.

30.2.4 Inhaled Corticosteroids

Anne Greenough and Anthony Milner

Educational Aims

- To describe methods of delivery of ICS to infants receiving respiratory support and the extent these systems achieve satisfactory penetration into the lung
- To review the efficacy and side effects of ICS compared to placebo and systemic steroids

Inhaled corticosteroids (ICS) have the potential to reduce the inflammatory changes which occur in the lungs, particularly of prematurely born infants, and lead to the development of bronchopulmonary dysplasia, importantly without the serious side effects associated with systemic corticosteroids. Techniques have been developed which ensure that adequate doses of ICS will penetrate into the lung. Although there is some information that ICS do reduce lung inflammation and improve lung function in the short term with few side effects, meta-analysis of 11 randomized controlled trials (RCTs) has demonstrated that they do prevent progression to bronchopulmonary dysplasia but may reduce the need for systemic steroids (Shah et al. 2012).

Bronchopulmonary dysplasia (oxygen dependency beyond 28 days after birth) remains a common complication of very premature delivery and is associated with chronic respiratory morbidity at follow-up. Meta-analyses of randomized trials have demonstrated that systemic administration of corticosteroids if given early (<96 h) or moderately early (7–14 days) is effective in facilitating weaning from the ventilator and reducing the incidence of oxygen dependence at 28 days of age and 36 weeks postmenstrual age (Halliday et al. 2009; Halliday et al. 2003). This benefit, however, comes at a considerable cost with increases in complications including systemic hypertension, gastrointestinal hemorrhage and perforation, and hyperglycemia. Even more worrying is the

association of systemically administered steroids and an increase in the incidence of neuromotor abnormalities at two years of age corrected for prematurity (Yeh et al. 1998). Indeed, meta-analysis of 20 RCTs including 2,064 infants demonstrated a significantly increased relative risk of cerebral palsy in those receiving early treatment (Doyle et al. 2005). As a consequence, there has been increasing interest in the possible role of ICS in the prevention and treatment of BPD, in the hope that ICS will be equally effective but without the associated side effects.

30.2.4.1 Methods of Delivery

The simplest delivery method is to activate a metered-dose inhaler (MDI) directly into the inspiratory tubing of the ventilator via a side port. The aerosol has particles which are predominantly between one and five microns, the ideal size for penetrating into the lower airways and lung, but does result in a high proportion of the MDI impacting on the inner lining of the ventilator tubing. Better results can be obtained by placing the side port 20 to 30 cm proximal to the patient manifold. A common method is to insert a spacer, e.g., AeroChamber, between the ventilator circuit and the endotracheal tube and activate the MDI immediately before the onset of mechanical inspiration. An alternative is to mount the MDI in a ventilation system consisting of either a self-filling resuscitation bag or an anesthetic rebreathing system and activate the MDI while manually ventilating the infant. For those receiving continuous positive airway pressure, the corticosteroids can be nebulized directly into a flow CPAP system (Smedsaas-Lofvenberg et al. 1999). An alternative is to feed the output of a jet or ultrasonic nebulizer into the inspiratory limb of the ventilator circuit, but both will tend to alter the pattern of ventilation delivered to the infant because of the increase in gas flow. The jet nebulizer output compared to an MDI contains a wider range of particle sizes, many of which will fail to reach the lower airways.

30.2.4.2 Efficacy of Methods of Delivery

Data on the efficacy of the different devices to deliver ICS to the lung are limited. Rozycki et al.

(1991) used a beclomethasone dipropionate MDI, a self-inflating bag, and a Tygon spacer to investigate the dose reaching a dummy lung. They found that 1.17 and 1.32 of the 50 µg were delivered via 3 and 3.5 mm endotracheal tubes with each activation of the MDI. As a consequence, they calculated that a neonate would require between one and six puffs per day. O'Callaghan and colleagues (1992) obtained similar results using radioactive labeled beclomethasone dipropionate delivered to a collapsible spacer by an MDI. The spacer was connected to an endotracheal tube and the spacer used to ventilate rabbits. They found that 3.3 % of the dose was deposited in the trachea and main airways and 1.9 % reached the lung. Arnon and colleagues (1992) investigated the deposition of budesonide on a filter at the entrance to a dummy lung ventilated by a standard neonatal ventilator. They compared two spacers, the AeroChamber and the Aerovent with MDIs, and two jet nebulizers, the MAD@ and the Ultravent. The AeroChamber delivered 14.2 % of the initial dose compared to 3.6 % with the Ultravent and less than 0.7 % with either of the jet nebulizers. These findings support the use of spacers rather than jet nebulizers for the delivery of ICS.

30.2.4.3 Therapeutic Uses of Inhaled Corticosteroids

Three possible therapeutic roles of inhaled corticosteroids have been investigated:

- (a) Reduction in the need for ventilatory support
- (b) Prevention of BPD
- (c) Reduction in the need for reintubation

30.2.4.3.1 Reduction in the Need for Ventilatory Support

30.2.4.3.1.1 Lung Function

There is limited information on the effects of ICS on lung function. In one study (Fok et al. 1999) of 53 ventilated infants, inhaled fluticasone compared to placebo produced a significant improvement in compliance within 3 days which persisted over the 14 days of treatment. There was also a significant though smaller reduction in respiratory resistance. A further study found that

improvements in functional residual capacity, the lung volume at the end of expiration, occurred after 7 days of inhaled corticosteroids compared to 36 h of systemic steroids (Dimitriou et al. 1997).

30.2.4.3.1.2 Lung Inflammation

It is well established that BPD is associated with an inflammatory response within the lungs. ICS appear less effective at reducing the inflammatory response in the first 2 weeks of ventilatory support than systemic steroids (Groneck et al. 1999).

30.2.4.3.1.3 Time to Extubation

A large study involving 233 preterm infants demonstrated that 20 % fewer infants required ventilatory support at the end of 4 weeks of treatment with inhaled beclomethasone compared to placebo (Cole et al. 1999), although not at 36 weeks postmenstrual age. In a smaller study 7 of 15 infants receiving systemic steroids were extubated after 14 days of therapy compared to 1–3 of those receiving increasing doses of inhaled beclomethasone. ICS were also less effective in reducing ventilatory requirements than systemic steroids as highlighted in a systematic review; indeed the ventilatory and oxygen requirements were 3.9 and 11 days longer (Shah et al. 2012). A Cochrane review concluded that ICS had no significant effect on time to extubation (Shah et al. 2012).

30.2.4.3.1.4 Need for Systemic Steroids

It had been suggested that the use of ICS is associated with a reduced need for systemic steroids (Cole et al. 1999), but the latest Cochrane review failed to confirm those results (Shah et al. 2012).

30.2.4.3.2 Prevention of BPD

The largest study involving 233 infants found that the incidence of oxygen dependency at 28 days was 43 % and 45 % and at 36 weeks 18 and 20 % for beclomethasone and placebo respectively (Cole et al. 1999). Meta-analysis of the results of 11 RCTs in which ICS were given before 2 weeks of age showed no reduction in BPD (Shah et al. 2012).

30.2.4.3.3 Reduction in Post-extubation Stridor and the Need for Reintubation

Currently systemic steroids are often given when stridor occurs after extubation of term and pre-term infants, particularly if this leads to reintubation. Nevertheless, meta-analysis of the results of two randomised trials in neonates found no overall statistically significant reduction in post-extubation stridor following administration of corticosteroids (Khhermani et al. 2011). Whether ICS have a role in the management of these infants after extubation has yet to be determined.

30.2.4.4 Side Effects

It is well established that although systemic steroids reduce intrapulmonary inflammation, aid weaning from ventilatory support, and reduce oxygen requirements at least in the short time, these benefits come at a considerable cost in terms of side effects.

As a result a number of studies have examined possible side effects produced by ICS, particularly on cortisol metabolism. Arnon et al. (1996) found that basal cortisol levels were within the normal range after inhaling budesonide. Suchomski and colleagues (Suchomski and Cummings 2002) measured the resting and ACTH cortisol response in infants receiving either 400 or 800 µg of beclomethasone each day. Although those receiving 800 µg had a reduced resting level, their response to ACTH was within normal limits. The only worrying report is that of Ng et al. (1998) who found that 1,000 µg of fluticasone reduced both the resting cortisol level and the response to ACTH. Studies have otherwise shown that ICS are very safe with no evidence of increases in the incidence of infection, hyperglycemia, hypertension, gastrointestinal bleeding, cataract, intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, retinopathy of prematurity, or patent ductus arteriosus (Shah et al. 2012).

Future Perspectives

- Research is needed to determine if the use of higher doses of ICS will be more effective without resulting in the side effects associated with systemic steroids.

Essential to Remember

- Inhaled corticosteroids can be given safely and relatively easily to ventilated infants with reasonable penetration into the lung.
- There is, however, no evidence that they reduce the incidence of BPD, but may have short-term benefits.

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Use of Potent Inhalational Anesthetic Agents During Mechanical Ventilation

31

Joseph D. Tobias

Educational Aims

- To understand the basic principles of the potent inhalational anesthetic agents including their chemical structures, physical properties, and factors regulating their uptake and distribution
- To understand the end-organ effects of the inhalational anesthetic agents including their adverse effect profile particularly as it pertains to the cardiovascular system
- To understand the therapeutic applications of the inhalational anesthetic agents in the pediatric ICU setting including sedation during mechanical ventilation and the treatment of refractory status asthmaticus and status epilepticus

- To understand the advantages and disadvantages of the various options for the delivery of the potent inhalational anesthetic agents in the pediatric ICU setting

31.1 History of the Potent Inhalational Anesthetic Agents

The clinical practice of inhalational anesthesia began in the 1840s with the demonstration of the efficacy of diethyl ether by Crawford Long and WTG Morton and nitrous oxide (N₂O) by Horace Wells. In 1946, Robbins reported the development of various fluorinated hydrocarbons (Robbins 1946). This work led to the synthesis in 1951 of fluroxene (2,2,2-trifluoroethyl vinyl ether), a fluorinated hydrocarbon, which was the first of this class of agents to be widely used in clinical practice (Krantz et al. 1953; Tucker et al. 1973; Johnston et al. 1973; Harris and Cromwell 1972). Halothane, a halogenated alkane, was introduced into clinical practice in 1956 (Raventos 1956). When compared with its predecessors, halothane offered several favorable properties including nonflammability, a favorable blood-gas partition coefficient, a favorable profile for inhalation induction including a rapid onset and limited pungency, bronchodilatation,

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relative cardiovascular stability, and a decreased incidence of nausea and vomiting. However, halothane's potential to elicit an immune-mediated hepatotoxicity especially in the adult population favored the development of additional agents with less hepatotoxicity.

Ongoing developments during the 1970s and 1980s led to the development of inhalational anesthetic agents of the methyl-ethyl ether class in an attempt to replace halothane. The methyl-ethyl ethers were favored over other compounds as they were stable, nonflammable, and effective general anesthetic agents. The substitution of fluorine for the various halides surrounding the carbon atoms led to greater stability and lower tissue solubility. This work led to the development of the modern class of inhalational anesthetic agents including enflurane, isoflurane, and eventually desflurane. The latter agents combined with the reintroduction of sevoflurane into clinical practice in the early 1990s comprise the currently used class of potent inhalational anesthetic agents. The following chapter reviews the end-organ effects of the potent inhalational anesthetic agents, reports of their applications in the pediatric ICU patient, and discusses special considerations for their administration in the pediatric ICU setting.

31.2 Principles of the Inhalational Anesthetic Agents

31.2.1 Chemical Structure

The inhalational anesthetic agents in common clinical use today include isoflurane, sevoflurane, and desflurane. Given the favorable profile of these three agents, the other two agents of the modern era of inhalational anesthesia, halothane and enflurane, are no longer used in clinical practice (see below). Although all five of the inhalational anesthetic agents produce similar hypnotic and sedative properties, they consist of two chemically distinct classes: alkanes (halothane) and ethers. Of the four ethers, isoflurane, enflurane, and desflurane are substituted methyl-ethyl ethers, and sevoflurane is a methyl-isopropyl

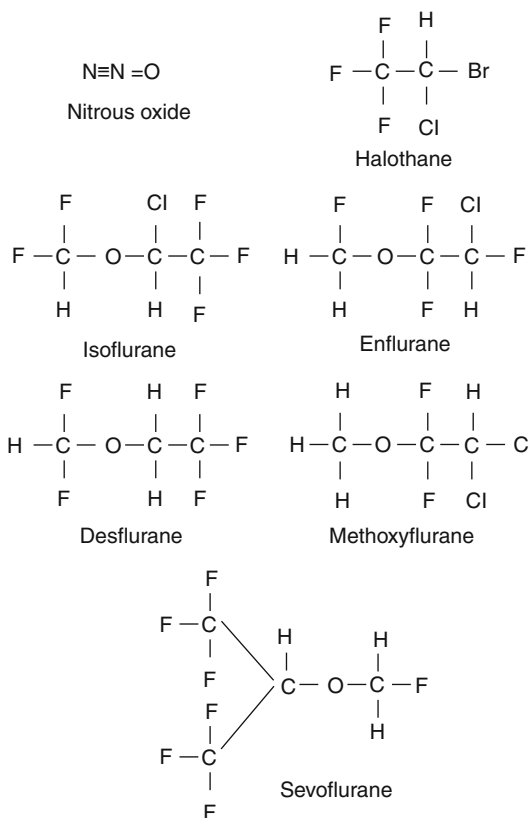


Fig. 31.1 The chemical structure of the potent inhalational anesthetic agents includes both an alkane (halothane) and ethers. Of the four ethers, isoflurane, enflurane, and desflurane are substituted methyl-ethyl ethers and sevoflurane is a methyl-isopropyl ether

ether (Fig. 31.1). The differential substitution of fluoride or chloride atoms around the carbon atoms of these molecules can significantly affect their physical properties, altering their blood-gas solubility, blood-fat solubility, and potency. The inhalational anesthetic agents are volatile liquids, meaning that they have the potential to transform into a vapor (Table 31.1). This property is used in clinical practice to deliver their agents in the gaseous or vapor state to the patient via the respiratory tract using a vaporizer (Fig. 31.2). The vaporizer allows the inspired concentration of the agent to be increased or decreased by adjusting the dial. As the concentration on the dial is increased, more of the gas flow is diverted through the vaporizer thereby increasing the inspired concentration of the inhalational

Table 31.1 Physical properties of the inhalational anesthetic agents

Inhalational anesthetic agent	Vapor pressure, mmHg at 20 °C	Blood-gas partition coefficient	Minimum alveolar concentration (%)
Halothane	243	2.54	0.76
Enflurane	175	1.91	1.7
Isoflurane	238	1.46	1.2
Sevoflurane	160	0.69	2
Desflurane	664	0.42	6

Fig. 31.2 Standard, agent-specific vaporizers on an anesthesia machine

anesthetic agent. Given that the vapor pressure varies from agent to agent, in today's clinical practice, there is a specific vaporizer calibrated for each of the various inhalational anesthetic agents. Prior to this technology, devices such as a copper kettle or a Vernitrol side arm were used to deliver the inhalational anesthetic agent. As these devices were not agent specific, calculations had to be carried out based on the barometric pressure, the agent in use, the vaporizer flow, and the total fresh gas flow to arrive at the inhaled concentration of the agent. Additionally, mistakes in anesthetic delivery could occur if two of the inhalational anesthetic agents were inadvertently mixed in the same vaporizer. Such problems are eliminated in today's practice by having agent-specific vaporizers that are color coded as well as key systems that prevent the filling of a vaporizer with the wrong agent. Of note is the specialized vaporizer required for the delivery of desflurane. As the vapor pressure of desflurane is three to four times that of the other inhalational anesthetic

agents and its boiling point is only 22.8 °C, its delivery requires a heated, pressurized vaporizer.

31.2.2 Uptake and Distribution

A unique aspect of the inhalational anesthetic agents which offers various advantages and disadvantages in the pediatric ICU setting is their administration via the respiratory tract. The onset of effect and duration of action of an inhalational anesthetic agent are determined by one its physical properties known as the blood-gas solubility coefficient. This coefficient describes how the anesthetic agent partitions itself between the blood and the alveolar gas when equilibrium is reached. In effect, this describes its solubility in the blood. The lower solubility in blood allows the alveolar concentration of the agent and hence the brain concentration of the agent to increase more rapidly than agents with a higher solubility in blood. As the goal is to achieve a specific

partial pressure of the inhalation anesthetic in the brain to create the desired effect, an agent with a high blood-gas solubility (partition) coefficient has a slower onset of action than an agent with a low blood-gas solubility coefficient. Likewise, the higher blood-gas solubility also results in a longer duration of action when administration of the agent is discontinued. Although this difference is most notable during the induction of anesthesia when agents with a low blood-gas solubility coefficient have a more rapid onset, the depth of anesthesia can also be adjusted more quickly with an agent that has a lower blood-gas solubility coefficient. Desflurane has the lowest blood-gas solubility coefficient and therefore the most rapid onset and offset of activity, followed in order by sevoflurane, isoflurane, enflurane, and halothane (Table 31.1).

Although the inhalational anesthetic agents are administered via the respiratory system, their delivery and distribution to the body tissues are governed by many of the same principles as medications administered via the intravenous route. The increase in the alveolar concentration of the agent is determined by the minute ventilation and the inspired concentration of the agent. The inhalational anesthetic agents are then taken up from the alveoli into the blood. Their uptake is dependent on their solubility in the blood (blood-gas partition coefficient), blood flow through the lungs (cardiac output), distribution of blood flow to the various tissue beds, and their solubility in these tissues (blood-tissue solubility coefficient). The end-capillary venous blood from the lungs which empties into the left atrium and eventually becomes the arterial blood leaving the left ventricle rapidly equilibrates with the alveolar concentration (Eger and Bahlman 1971). In turn, the arterial concentration of the inhalational anesthetic agent equilibrates with the brain tissue to provide the anesthetic effect. Given these principles, the alveolar concentration of the agent parallels the brain tissue concentration. This occurs given the high blood flow to the brain compared to other organs. These principles describe why agents such as desflurane and sevoflurane that are relatively insoluble in blood and have a low blood-gas solubility coefficient result in a more

rapid rise in the alveolar concentration and therefore the most rapid onset of action. Although these effects may be of limited importance when these agents are used in the PICU setting, they govern the onset of action during the induction of anesthesia in the operating room setting.

The increase in the alveolar concentration depends on the difference between the delivery of the agent to and its removal from the alveolus. Delivery is controlled by the inspired concentration of the agent and the patient's minute ventilation. The removal of these agents from the alveoli is dependent on the solubility of the agent in the blood (blood-gas partition coefficient), the pulmonary blood flow, and the concentration of the agent in the mixed venous blood. Therefore, the rise in the alveolar concentration of the inhalational agent may be altered by the presence of congenital heart disease and right-to-left or left-to-right shunts. In a patient with a left-to-right shunt, blood with a high concentration of the inhalational anesthetic agent returns from the lung and enters the left atrium. This blood then recirculates through the lungs through the left-to-right shunt, thereby increasing the mixed venous oxygen tension of the inhalational anesthetic agent more rapidly than the normal. This accelerates the rise in the alveolar concentration and thereby the onset of action of the agent. In a patient with a right-to-left shunt, the opposite effect occurs with a delayed onset of action of these agents.

31.2.3 Potency (Minimum Alveolar Concentration or MAC)

The potency of an inhalational anesthetic agent is measured by using the principle of MAC (minimum alveolar concentration). MAC is defined as the end-tidal concentration (percentage) of the inhalational anesthetic agent in 1 atm that prevents 50 % of patients from moving in response to a surgical stimulus. It mirrors brain partial pressure and therefore allows for comparison between these agents. The most potent of the agents will have the lowest MAC value as less is required to produce a given clinical effect

(Table 31.1). Halothane is the most potent of the inhalational anesthetic agents with a MAC of approximately 0.76 % followed in order by isoflurane (1.2 %), enflurane (1.7 %), sevoflurane (2 %), and desflurane (6 %). Both patient-related factors and the concomitant administration of other medications can affect MAC. Medications which lower the MAC of the inhalational anesthetic agents include opioids, α_2 -adrenergic agonists, and benzodiazepines. Other factors that may affect MAC include age, pregnancy, and central nervous system disorders. MAC is lower in preterm infants, increases in term infants, and then decreases slightly with advancing age (Le Dez and Lerman 1987; Gregory et al. 1969). As it would be undesirable to have 50 % of patients moving during surgical procedures, 1.5–2.0 MAC of an inhalational anesthetic agent may be administered intraoperatively during anesthetic care. Alternatively, a lower concentration agent of the agent (1.0–1.5 MAC) may be combined with other agents such as nitrous oxide (N_2O), opioids, or intravenous anesthetic agents to provide maintenance anesthesia. Another term, MAC awake describes the partial pressure (end-tidal concentration) at which most patients will open their eyes and awake from the general anesthetic. This is generally 0.3–0.4 MAC. In the pediatric ICU setting, when these agents are used for various therapeutic purposes, the concentration required to achieve the desired effect will vary considerably depending on the clinical scenario, the indication for its use, the patient's status, and the duration of administration.

31.3 End-Organ Effects

As with any medication used in the pediatric ICU setting, the inhalational anesthetic agents may have deleterious effects on physiologic functions. Unlike their earlier predecessors, all of the inhalational anesthetic agents in current clinical use are nonflammable and nonexplosive. They provide the prerequisites of a general anesthetic including amnesia, analgesia, skeletal muscle relaxation, and to some extent control of the sympathetic nervous system. Although the

inhalational anesthetic agents share these effects on the central nervous system, in other regards, given the variances in their chemical structure, their adverse effects on end-organs may be quite different.

31.3.1 Central Nervous System

Recent work suggests that the inhalational anesthetic agents stabilize critical proteins, possibly receptors of neurotransmitters particularly those that have an inhibitory effect in the CNS including the γ -amino butyric acid (GABA) system, the same system involved in the CNS effects of benzodiazepines, barbiturates, and propofol (Eckenhoff et al. 2005). Given their depressant effects on the CNS, the inhalational anesthetic agents cause a dose-related decrease in CNS activity, reduce the cerebral metabolic for oxygen, and depress electroencephalographic (EEG) activity. In contrast to their usual depressant effects on the EEG pattern, in specific circumstances, both enflurane and sevoflurane can activate the EEG and produce EEG evidence of epileptiform activity (Eckenhoff 1998). Although these EEG changes are rarely of clinical significance, they are also occasionally accompanied by motor manifestations suggestive of seizure activity such as rhythmic movements of the extremities or tonic posturing. This EEG activation generally occurs during the rapid increase in the alveolar concentration of the agent or the administration of high inhaled concentration such as the inhalational induction of anesthesia when inspired concentration of 6–8 % sevoflurane is commonly used. In this situation, EEG activation is enhanced by hyperventilation and the development of hypocarbia. Clinical practice also suggests that such activation may be more common in children with abnormal neurologic function or underlying disorders of the CNS. Despite this property, as outlined below, all of the inhalational anesthetic agents including sevoflurane depress EEG activity and have been used in the treatment of status epilepticus.

Although the inhalational anesthetic agents decrease the cerebral metabolic rate for oxygen,

they increase cerebral blood flow (CBF) in a dose-dependent manner via a reduction in cerebral vascular resistance. This cerebral vasodilatation may elevate intracranial pressure (ICP) in patients with compromised intracranial compliance. Additionally, the hemodynamic effects may lower mean arterial pressure (MAP) which coupled with the increase in ICP may further decrease cerebral perfusion pressure (CPP) (Sponheim et al. 2003). The adverse effects on ICP are least with isoflurane, minimized by limiting the concentration to 1.0 MAC, and are blunted by hyperventilation leading to hypocarbia (PaCO_2 of 25–30 mmHg) (Adams et al. 1981; Drummond et al. 1986). However, given these effects both directly on ICP and indirectly on CPP via the effects on MAP, these agents should be used cautiously in patients at risk for alterations in ICP or those who may not tolerate decreases in CPP. In addition to these effects on the CNS, the potent inhalational anesthetic agents depress neuromuscular activity and enhance the effect of non-depolarizing neuromuscular blocking agents.

31.3.2 Airway, Respiratory System, and Control of Ventilation

In the practice of pediatric anesthesia, infants and children frequently present to the operating room without intravenous access. As such, anesthesia is induced by the inhalation of increasing concentrations of an inhalational anesthetic agent. In clinical practice for decades, the only agent that was nonpungent to the airway and therefore suitable for this purpose was halothane. However, given its adverse effects on hemodynamic function and the potential to cause morbidity and even mortality, the search continued for alternative agents which led to the introduction of sevoflurane into clinical practice in the 1990s. Given its limited effects on myocardial contractility and chronotropic function when compared with halothane, sevoflurane became the preferred agent for the inhalational induction of anesthesia with the eventual removal of halothane from anesthetic practice. Such a move was prompted by data implicating halothane as the primary agent

responsible for the majority of cardiac arrests during general anesthesia in infants and children (Murray et al. 2000). Additionally, given its lower blood-gas partition coefficient, the speed of induction is faster and recovery more rapid with sevoflurane than with halothane.

The inhalational anesthetic agents result in a dose-dependent depression of ventilatory and cardiovascular function. These effects are modified by the coadministration of other medications as well as the presence of comorbid disease processes. With an increasing inspired concentration and anesthetic depth, there is a progressive decrease in alveolar ventilation characterized by a reduction in tidal volume and an increase in PaCO_2 in spontaneously breathing patients. Clinically this is manifested by a rightward shift of the CO_2 response curve. The inhalational anesthetic agents also blunt the normal ventilatory responses to hypercarbia and hypoxia (i.e., the “hypoxic drive” is depressed). Additionally, these agents may impair oxygenation especially in patients with pulmonary parenchymal disease or atelectasis through the inhibition of hypoxic pulmonary vasoconstriction (HPV) (Benumof et al. 1987). As with many of the other physiologic effects, the impact on HPV and hence oxygenation is dose dependent with limited effects at a MAC of ≤ 1 . Beneficial effects on the airways include a direct effect on bronchial smooth muscle with a decrease in the cytoplasmic calcium availability thereby result in bronchodilatation (Hirshman et al. 1982). Given this effect, the inhalational anesthetic agents have been used effectively outside of the OR for the treatment of patients with refractory status asthmaticus (see below). The airway effects result from both a depression of airway reflexes and a direct effect on the airway smooth musculature (Hirshman et al. 1982; Warner et al. 1990). Although these effects are shared by all of the inhalational anesthetic agents, animal data suggest that the effect may be greatest with halothane (Katoh and Ikeda 1994). However, given its negative inotropic effects and the potentially greater morbidity and mortality with its intraoperative use when compared with other agents, halothane is no longer used in clinical practice.

31.3.3 Cardiovascular System and Hemodynamic Effects

The inhalational anesthetic agents share some hemodynamic effects including a decrease of MAP, a depression of myocardial contractility, and a reduction of myocardial oxygen consumption. The decrease in MAP and cardiac output that occurs with these agents may secondarily affect the function of other end-organ by decreasing perfusion. For example, the MAP reduction may lead to a reduction of CBF as well as hepatic and renal perfusion. Although these vascular beds autoregulate within a specific MAP and thereby maintain flow, these autoregulatory effects may be blunted to some extent by the inhalational anesthetic agents. As with the effects on the control of ventilation, the effects on hemodynamic function and cardiac output are dose dependent. Additionally, these effects are modified by the patient's intravascular status, underlying myocardial function, and the coadministration of other anesthetic agents.

Although the inhalational anesthetic agents in general depress hemodynamic and cardiovascular function, the specific changes in cardiac output, systemic vascular resistance, and heart rate vary from agent to agent. Isoflurane and desflurane have limited effects on inotropic function and primarily result in vasodilatation with a decrease in systemic vascular resistance and MAP. The vasodilatation results in reflex tachycardia. Rapid increases in the inspired concentration of desflurane may also stimulate the sympathetic nervous system and thereby further increase heart rate. A decrease in heart rate is commonly seen with sevoflurane administered at lower inspired concentrations (0.5–1 MAC), while inspired concentrations greater than 1 MAC may decrease SVR and result in a reflex tachycardia. However, the reflex tachycardia is generally not to the extent seen with isoflurane and desflurane. Halothane on the other hand had little or no effect on SVR and resulted primarily in direct negative chronotropic and inotropic effects resulting in a decreased heart rate and decreased cardiac output.

As the primary hemodynamic effects of isoflurane and desflurane are peripheral vasodilatation,

there is a decrease in afterload (SVR) which results in an increase in cardiac output as opposed to the decrease in cardiac output that occurs with sevoflurane, halothane, or enflurane. The reflex tachycardia which frequently occurs with isoflurane and desflurane can increase myocardial oxygen demand, while vasodilatation may lower diastolic blood pressure, thereby reducing myocardial perfusion pressure and myocardial oxygen delivery. Given the imbalance that may occur between myocardial oxygen delivery and consumption, theoretical concerns have been raised regarding the potential for myocardial ischemia in at risk patients. Additionally, with isoflurane, a coronary steal phenomenon may result as there may be vasodilatation of normal coronary vasculature with no effect in areas of fixed coronary stenosis. Due to these concerns, isoflurane should be used cautiously in patients at risk for myocardial ischemia or in patients who are unable to tolerate tachycardia and a decrease in systemic vascular resistance. This may also be a consideration in patients with residual or palliated congenital heart disease in whom alterations in the systemic and pulmonary vascular resistance may significantly affect the ratio of pulmonary to systemic blood flow. These effects on heart rate and SVR may be further aggravated by the concomitant use of other medications or comorbid disease processes.

A final issue of concern with halothane was the potential to sensitize the myocardium to arrhythmogenic effects of endogenous or exogenous catecholamines. This effect was related to its primary chemical structure and is generally not seen with the other inhalational anesthetic agents which are not in the alkane group. This effect can precipitate dysrhythmias especially when there is associated hypercarbia, when used in conjunction with other medications (aminophylline), or in the presence of high circulating catecholamine.

31.3.4 Hepatic and Renal Function

The stability and eventual metabolic fate of the inhalational anesthetic agents is determined by their chemical structure. In general, the newer

inhalational anesthetic agents have been modified and developed to undergo little or no metabolism thereby limiting the potential adverse effects related to their metabolic products. The latter is especially true of the newest of these agents, desflurane. Fifteen to twenty percent of halothane is recovered as metabolites compared to 3–5 % for sevoflurane, 2–3 % for enflurane, 0.2 % for isoflurane, and less than 0.1 % for desflurane. In addition to the parent compound, metabolic products from metabolism by the P_{450} system may also be responsible for the toxicity of these agents. Of significant concern with many of the older inhalational anesthetic agents including halothane was the potential for the development of hepatotoxicity. Although described shortly after the introduction of these drugs into clinical practice, the mechanism of the hepatic injury was later determined to be related to an immune-mediated reaction following exposure to halothane, enflurane, isoflurane, or desflurane (Satoh et al. 1986; Kenna et al. 1988; Subcommittee on the National Halothane Study of the Committee on Anesthesia 1966; Kenna and Jones 1995; Brown and Gandolfi 1987). The metabolic product of the inhalational anesthetic agents, trifluoroacetic acid (TFA), can act as a hapten, binding to hepatocytes and inducing an immune-mediated hepatitis. Although described primarily with halothane, given its higher metabolic processing and thereby a greater production of TFA, there have been anecdotal reports of hepatitis with enflurane, isoflurane, and even desflurane (Kenna and Jones 1995; Brown and Gandolfi 1987; Pohl et al. 1988). However, although 3–5 % of sevoflurane is metabolized, its metabolic pathway is different from the other agents and does not result in the production of TFA.

Clinically, the hepatotoxicity associated with the inhalational anesthetic agents manifests in one of two ways, a mild form and a fulminant form. As mentioned previously, given its greater metabolism, hepatotoxicity occurs primarily with halothane. As such, the majority of the information regarding the inhalational anesthetic agents and hepatotoxicity data related to halothane. The mild form affects 20 % of adults who receive halothane while the fulminant form (halothane

hepatitis) occurs in 1 of every 10,000 adult patients following halothane anesthesia. The fulminant form results in massive hepatic necrosis with hepatic insufficiency or failure with a mortality rate of 50–75 %. The majority of the patients (up to 95 %) who develop the fulminant form have had a prior exposure to halothane. In fact, the most important predictive factor for halothane hepatotoxicity is prior multiple anesthetic exposure at short intervals. Additional risk factors include female gender, middle age, obesity, and factors which induce the hepatic microsomal enzymes. The latter may include chronic ethanol ingestion and medications such as isoniazid and the barbiturates. Given the concerns of halothane hepatitis, there was limited use of this agent in the adult population following the introduction of isoflurane and enflurane into clinical practice, but it remained the most commonly used inhalational agent in infants and children until the early 1990s when sevoflurane was introduced. Despite its occurrence in adults, halothane hepatitis was exceedingly uncommon in children (1/200,000) (Wark 1983; Warner et al. 1984). The immunologic mechanism of halothane hepatitis was later shown to be related to an immunologic reaction against the metabolic product, TFA. TFA can act as a hapten binding to hepatocytes and inducing an autoimmune hepatic injury. Because cross-sensitization may occur, all of the inhalational anesthetic agents except sevoflurane should be avoided in patients who have an unexplained postoperative hepatic injury following exposure to an inhalational anesthetic agent. The diagnosis of hepatic injury following inhalational anesthetic agent use can be confirmed with serologic demonstration of the anti-TFA antibody in the sera of patients.

The inhalational anesthetic agents may also result in nephrotoxicity related to either release of fluoride during the metabolism of the parent compound or the production of toxic metabolic by-products. Several of the inhalational anesthetic agents are highly substituted around their carbon atoms with the halide, fluoride. As such, dependent on their metabolic fate, fluoride may be released in significant quantities especially during a prolonged anesthetic or the administration

of a high concentration of the agent. Fluoride concentrations greater than 50 $\mu\text{mol/L}$ can result in decreased glomerular filtration rate and renal tubular resistance to vasopressin with nephrogenic diabetes insipidus. One of the earlier of the inhalational anesthetic agents, methoxyflurane, was eventually eliminated from clinical practice due to its potential for nephrotoxicity due to fluoride release. Similar concerns were demonstrated with enflurane. Although a limited amount of enflurane is metabolized when compared with methoxyflurane, its content of fluoride is high enough that serum fluoride concentrations can increase with prolonged administration (Mazze et al. 1977).

Two separate concerns regarding the potential nephrotoxicity of sevoflurane have been raised in the literature: fluoride release during metabolism and the production of the metabolic by-product, compound A (see below). Although high levels of serum fluoride may occur following the prolonged administration of sevoflurane, clinical signs of nephrotoxicity are extremely rare. This is postulated to be the result of the low blood-gas partition coefficient of sevoflurane and its rapid elimination from the body or the fact that sevoflurane unlike methoxyflurane does not undergo metabolism in the kidney, but only in the liver. Therefore, unlike methoxyflurane, there is no local renal release of fluoride.

The second concern raised regarding potential nephrotoxicity of sevoflurane is related to the production of a unique metabolite, a vinyl ether also known as compound A. Compound A is produced during the metabolism of sevoflurane and its reaction with the CO_2 soda lime in the carbon dioxide absorber of the anesthesia machine (Morio et al. 1992; Frink et al. 1992). The safe concentration of compound A is unknown in humans as is the mechanism of renal injury (Mazze 1992). Compound A concentrations are increased by several factors including a high inspired concentration of sevoflurane, low fresh gas flows through the system (less than 2 L/min), increasing temperatures of the soda lime canister, decreased water content of the CO_2 absorbant, high concentrations of potassium or sodium hydroxides in the CO_2 absorbant, and long

duration of anesthesia. Although clinical data suggest that there is no significant clinical risk of nephrotoxicity during the intraoperative administration of sevoflurane, there are no data regarding compound A concentrations during the prolonged administration of sevoflurane in the pediatric ICU setting. However, given that CO_2 absorbers are not generally used when the potent inhalational anesthetic agents are administered in the ICU setting, there are likely to be no concerns regarding compound A.

31.3.5 Miscellaneous End-Organ Effects

All of the potent inhalational anesthetic agents are triggering agents for malignant hyperthermia (MH). MH is an inherited disorder of muscle metabolism with an estimated incidence of 1:15–20,000 in adults and 1:50,000 in infants and children. The primary cellular defect resides in the ryanodine calcium channel in the sarcoplasmic reticulum. Following exposure to any of the inhalational anesthetic agents or the depolarizing neuromuscular blocking agent, succinylcholine, dysfunction of this ion channel results in ongoing and exaggerated calcium release into the cytoplasm. The ongoing increase in cytoplasmic calcium results in ongoing muscle contraction and a hypermetabolic state. The clinical signs and symptoms include tachycardia, hyperthermia, hypercarbia, muscle rigidity, and rhabdomyolysis. The rhabdomyolysis results in hyperkalemia and acidosis. Treatment includes prompt recognition, removal of the triggering agent, and the administration of dantrolene. Additional therapy is aimed at the correction of the hyperkalemia and acidosis. Without appropriate therapy including the administration of dantrolene, mortality exceeds 90 %.

Additional concerns with the inhalational anesthetic agents include anecdotal reports of carbon monoxide (CO) toxicity, cost issues, and alterations of the metabolism of other medications. Reports of CO toxicity have typically occurred in a scenario that involves the first case in the operating room on a Monday morning.

The release of carbon monoxide results from the interaction of the inhalational anesthetic agent (most commonly desflurane) and the CO₂ absorbant, which has become desiccated because of no use over the weekend (Woehlck 1999; Baum et al. 1995). In vitro studies have demonstrated that CO can be produced by the interaction of desflurane and isoflurane, but not sevoflurane, and the CO₂ absorbant (Fang et al. 1995). CO production increases with specific characteristics of the CO₂ absorbant including decreased water content, increased temperature, and increased concentration of potassium hydroxide. As with compound A issues, since CO₂ absorbants are not generally used in the pediatric ICU setting, this is not likely to become a clinical issue. Additionally, this problem is thought to occur only when the soda lime has become desiccated from the prolonged administration of a high gas flow.

The inhalational agents alter hepatic blood flow and may thereby affect the metabolism of other medications that are administered in the ICU including lidocaine, β -adrenergic antagonists, benzodiazepines, and local anesthetic agents (Reilly et al. 1985). These potential interactions and their clinical effects must be considered when pharmacologic agents are coadministered with the inhalational anesthetic agents.

31.4 Applications in the Pediatric ICU Setting

The inhalational anesthetic agents are administered everyday during surgical procedures worldwide to provide general anesthesia and ensure intraoperative amnesia and analgesia. The clinical characteristics of these agents which make them useful intraoperatively (e.g., rapid onset, rapid awakening upon discontinuation, and ease of control of the depth of sedation) may also make them useful in the pediatric ICU setting. The physiologic effects which include bronchodilatation and anticonvulsant properties may make them effective therapeutic agents in refractory cases of status asthmaticus and status epilepticus.

31.4.1 Procedural Sedation

In addition to their use in the operating room or off-site using standard anesthesia machines, there are limited reports regarding the administration of inhalational anesthetic agents for procedural sedation with novel delivery devices. Several studies demonstrate the efficacy of methoxyflurane as an agent for procedural sedation in various clinical scenarios (Marshall and Ozorio 1972; Babl et al. 2006; 2007). Babl et al. reported the use of methoxyflurane as a prehospital analgesic in a cohort of 105 patients who ranged in age from 15 months to 17 years (median 15 years) (Babl et al. 2006). The indication for analgesia included extremity injuries (81.9 %), abdominal pain (6.7 %), head or facial injury (4.8 %), burns (3.8 %), or multiple trauma (2.8 %). Methoxyflurane was administered by paramedics during the prehospital period using a Penthrox™ inhaler (Medical Developments International, Victoria, Australia), a tubular, handheld device which is primed with liquid methoxyflurane (3 mL) and provides 25–30 min of administration. The device has a 22-mm mouthpiece which can also be fitted with a standard resuscitation mask to aid in delivery in younger patients who cannot use the mouthpiece. The device also has a one-way valve to prevent blowback into the wick which holds the liquid methoxyflurane and an oxygen inlet for the delivery of supplemental oxygen if needed. There is also a dilutor hole which allows the delivery of varying concentrations of methoxyflurane from 0.1 to 0.2 % with the hole open to 0.3–0.4 % with hole occluded. The device is held by the patient and methoxyflurane is delivered as the patient breathes in and out through the device. Public awareness of the device has increased given its use to provide analgesia following an injury and during transport of a participant of the reality television show, *Survivor*, which is broadcast in the USA (<http://www.cbs.com/primetime/survivor2/show/episode06/story.html>). In the study of Babl et al. (2006), 96 of the patients received a single 3-mL dose and 9 received 2 doses of methoxyflurane. The inhalational anesthetic agent was administered using the Penthrox™ inhaler; however, in

nine patients (generally those less than 5 years of age), a mask was attached to the inhaler instead of having the patient hold the device in their mouth. Ten patients received additional analgesia with intravenous morphine. Pain scores (using a scale of 0–10) decreased from a mean of 7.9–4.5 at 2–5 min and 3.2 at 10 min following the administration of methoxyflurane. Acceptable analgesia was achieved in 88.5 % of the patients as judged by the paramedics and 87 % of the patients as judged by self-report scores. No serious adverse effects were noted.

Although methoxyflurane was used extensively as a general anesthetic agent and for procedural sedation during the 1960s and 1970s, with the development of newer agents and recognition of the potential for nephrotoxicity with methoxyflurane as fluoride and oxalic acid are released during its metabolism, its use decreased markedly and it is no longer available for clinical use in the United States (Mazze 2006). The technique of methoxyflurane using the Pentrox™ inhaler is licensed in Australia for self-administration to conscious, hemodynamically stable patients with trauma-associated pain and for procedural sedation. In some areas of Australia, it is the most commonly used analgesia agent during the pre-hospital transport of patients, its advantages being not only its efficacy but also its administration via the inhalation route using relatively simple technology.

Sevoflurane has also been administered outside of the operating room setting for procedural sedation. Sury et al. administered sevoflurane via a nasal cannula to provide sedation during magnetic resonance imaging in 13 infants with a median post-conceptual gestational age of 46 weeks (range 40–70 weeks) and a median weight of 4.4 kg (range 3.3–6.5 kg) (Sury et al. 2005). Sevoflurane was delivered from a standard anesthesia machine vaporizer using a flow rate of 2 L/min and delivered via nasal cannulae. The technique was successful in 12 infants using a median maximum inspired sevoflurane concentration of 4 % (range 4–8 %). One infant desaturated to 85 % and required repositioning of the head to maintain a clear airway. With either the use of methoxyflurane using the Pentrox™

inhaler or the administration of sevoflurane via a nasal cannula, there may be concerns regarding environmental pollution and healthcare worker exposure as scavenging may not be feasible.

For procedural “sedation” you should also add a discussion on N₂O (this is very common at least in Europe) – this would be a very, very lengthy topic and likely one that is not particularly relevant to the main impetus of the book (mechanical ventilation); if you disagree, please let me know and I can come up with something.

31.4.2 Sedation During Mechanical Ventilation

Although there are several options available for the provision of sedation in the ICU setting, there remains interest in the potential application of the inhalational anesthetic agents for the provision of sedation during mechanical ventilation. To date, the majority of the applications of these agents for sedation in the ICU setting have been in the adult population. In this population, the majority of the reports have outlined favorable experiences with potential advantages over commonly used agents including benzodiazepines or propofol (Kong et al. 1989; Millane et al. 1992; Meiser et al. 2003; Breheny and Kendall 1992). Although many of the studies regarding the use of the inhalational anesthetic agents for sedation are relatively recent, the technique is definitely not a novel idea. In 1969, Prys-Roberts et al. reported the use of these agents in adults to provide sedation during mechanical ventilation and to control the autonomic hyperactivity associated with tetanus (Prys-Roberts et al. 1969). More recently, there has been renewed interest with the use of the inhalational anesthetic agents to provide sedation during mechanical ventilation in the adult population and anecdotal experience reported in the pediatric-aged patient.

Researchers at Boston Children’s Hospital reported experience with the administration of isoflurane for sedation during mechanical ventilation in a cohort of ten pediatric patients, who ranged in age from 3 weeks to 19 years (Arnold et al. 1993a). The duration of isoflurane use varied from 29 to

769 h (245 ± 225 h) in the ten patients. The total number of MAC-hours ranged from 13 to 497 (131 ± 154 MAC-hours). Sedation was initiated with isoflurane at an inspired concentration of 0.5 % and adjusted in 0.2 % increments as needed. An assessment of the depth of sedation was performed in seven patients with adequate sedation noted 75 % of the time, excessive sedation 4 % of the time, and inadequate sedation 21 % of the time. Transient changes in renal and hepatic function were noted in some patients; however, in the five patients who received isoflurane for at least 96 MAC-hours, there were no differences in blood urea nitrogen, serum creatinine, osmolality, bilirubin, and alanine aminotransferase before the start of isoflurane and following a total of 96 h of administration. The plasma fluoride concentration correlated directly with the duration of isoflurane administration with a mean peak concentration of 11.0 ± 6.4 $\mu\text{mol/L}$. The maximum fluoride concentration noted in any of the patients was 26.1 $\mu\text{mol/L}$, which occurred after 441 MAC-hours of isoflurane. One patient required fluid administration for the treatment of hypotension. When the isoflurane was discontinued, five patients manifested signs and symptoms of withdrawal including marked agitation and non-purposeful movements. All had received more than 70 MAC-hours of isoflurane. Similar issues with tolerance, dependency, and withdrawal following the prolonged administration of isoflurane in the pediatric ICU have been reported by other investigators (Kelsall et al. 1994; Arnold et al. 1993b).

Anecdotal experience with the use of isoflurane for sedation in the pediatric ICU in other clinical scenarios has been reported by various authors. Kelsall et al. retrospectively reviewed their experience with sedation using isoflurane in children requiring endotracheal intubation and mechanical ventilation due to upper airway issues (laryngotracheobronchitis or epiglottitis) (Spencer et al. 1991). Although isoflurane was effective, patients who required prolonged administration of isoflurane manifested reversible neurologic dysfunction including ataxia, agitation, hallucinations, and confusion after extubation and cessation of isoflurane.

31.4.3 Treatment of Status Asthmaticus

In addition to their anesthetic properties, the inhalational anesthetic agents are also potent bronchodilators. The initial reports of the treatment of status asthmaticus with the older generation of the inhalational anesthetic agents including tribromethanol, cyclopropane, and ether first appeared in the literature in the 1930s (Fuchs 1937; Meyer and Schotz 1939; Robertson et al. 1985). Given the successes outlined in the initial reports, the modern-day inhalational anesthetic agents including halothane, isoflurane, and enflurane were subsequently used for the treatment of adults requiring mechanical ventilation for refractory status asthmaticus (Schwartz 1984; Bierman et al. 1986; Parnass et al. 1986; Saulnier et al. 1990; Echeverria et al. 1986).

Although anecdotal, there are several reports in the literature detailing beneficial effects of the administration of inhalational anesthetic agents in children with refractory status asthmaticus (Rosseel et al. 1985; Revell et al. 1988; Tobias and Garrett 1997; O'Rourke and Crone 1982; Johnston et al. 1990). The previously discussed study of Arnold et al. 1993b, which was primarily intended to present the use of the inhalational anesthetic agents as primary agents for sedation during mechanical ventilation, included four pediatric patients who received isoflurane not only for sedation but also for bronchodilation in the treatment of status asthmaticus. However, as the report focused on the sedative properties of the inhalational anesthetic agents, no additional details are provided regarding the effects of isoflurane on airway and pulmonary mechanisms. The largest case series reported to date outlining the use of inhalational anesthetic agents in the treatment of status asthmaticus in the pediatric population included six patients who ranged in age from 14 months to 15 years (Wheeler et al. 2000). Isoflurane was used successfully in six patients when their status asthmaticus failed to respond to conventional therapy. In addition to reporting their experience

in this clinical scenario, the authors also presented their protocol for the use of isoflurane in the treatment of status asthmaticus. Entry criteria for the initiation of therapy with isoflurane included patients who required endotracheal intubation and mechanical ventilation, a PIP ≥ 40 cmH₂O, and failure of conventional therapy including intravenous corticosteroids, magnesium, anticholinergic therapy, and terbutaline at doses ≥ 5 $\mu\text{g/kg/min}$. Isoflurane was administered using a Servo 900D ventilator with an attached vaporizer. Isoflurane was started at an inspired concentration of 1–2 % and increased by 0.1 % every 5–10 min with the goal of achieving adequate ventilation with a PIP ≤ 35 cmH₂O. They also recommend discontinuing neuromuscular blocking agents and intravenous sedatives once the isoflurane concentration had reached an inspired concentration of 1 %. Other therapies for status asthmaticus should be continued as their mechanism of action is different from the potent inhalational anesthetic agents. They recommended monitoring with end-tidal CO₂, invasive central venous and arterial catheters, and consideration of the use of inline monitoring of isoflurane concentration.

More recently, anecdotal success has also been reported with the use of sevoflurane to treat status asthmaticus. Watanabe et al. reported the use of sevoflurane to treat postoperative bronchospasm in a 3-month-old infant (Watanabe et al. 2008). Despite therapy with inhaled β -adrenergic agonists, intravenous aminophylline, and corticosteroids, there was progressive deterioration of the patient's respiratory status with an increase in the PIP to 50–60 cmH₂O and decreasing oxygen saturation. Sevoflurane was started at an inspired concentration of 5 % which resulted in improvements in gas exchange and a decrease of the PIP. The inspired concentration was subsequently decreased to 2–3 %, but efforts to wean the sevoflurane failed and the therapy was continued for a total of 94 h. At that time the patient's status had improved and the sevoflurane was eventually discontinued. Serum inorganic fluoride concentration on day 3 of therapy was 24.2 $\mu\text{mol/L}$.

31.4.4 Treatment of Status Epilepticus

As noted above, in addition to their sedative and amnestic properties, the inhalational anesthetic agents produce dose-dependent changes in the EEG with an initial decrease in the amplitude and frequency of the EEG during the administration of sub-MAC concentrations which progresses to increasing periods of electrical silence (burst suppression) as the concentration is increased to 2–2.5 MAC. Anesthesia with either halothane or enflurane decreases the number of epileptogenic spikes in patients with a history of epilepsy (Opitz et al. 1982). Isoflurane has been effective in the control of postoperative status epilepticus (SE) in adult patients following neurosurgical procedures near the motor strip even when conventional anti-convulsant agents had failed (Sakaki et al. 1992). When evaluating the advantages and disadvantages of using the inhalational agents or the barbiturates, the authors cited specific advantages of isoflurane including less effect on cardiovascular function and fewer problems with maintaining a steady-state serum concentration. The potential role of the inhalational anesthetic agents in the treatment of SE is also supported by animal studies (Fukuda et al. 1996). In protocols for refractory SE reported from the literature, treatment regimens include the use of general anesthesia with the administration of inhalational anesthetic agents (Delgado-Escueta et al. 1982; Haafiz and Kissoon 1999). As with the reports describing the use of inhalational anesthesia for the treatment of refractory status asthmaticus, reports regarding the use of these agents for SE are primarily anecdotal involving isolated case reports or small case series with a limited number of pediatric-aged patients (Hughes et al. 1992; Hilz et al. 1992; Meeke et al. 1989; Ropper et al. 1986; Kofke et al. 1985; Mirsattari et al. 2004). Despite the anecdotal nature of these reports, there is universal agreement from these anecdotes regarding the potential efficacy of the inhalational agents in this scenario. These reports have included various inhalational agents including halothane, isoflurane, and desflurane in the treatment of SE that is

refractory to conventional therapy including benzodiazepines, barbiturates, and phenytoin.

The first report of the use of isoflurane for the treatment of SE in a pediatric patient was published in 1985 (Kofke et al. 1985). The same authors subsequently reported the largest clinical series regarding the use of potent inhalational anesthetic agents in the treatment of SE in pediatric patients (Kofke et al. 1989). In this cohort of nine patients, six were pediatric-aged ranging from 2 to 13 years old. The etiology of the SE included organophosphate toxicity ($n=1$), status post hepatic transplantation ($n=1$), status post arteriovenous malformation resection ($n=2$), and idiopathic ($n=2$). In all patients, conventional therapy with at least phenobarbital, phenytoin, and benzodiazepines had failed to control SE. Isoflurane controlled SE in all patients, the only adverse effect being hypotension which was treated with isotonic fluids and vasopressors.

31.5 Special Aspects of Delivery in the Pediatric ICU Setting

Despite their potential benefit in several difficult clinical scenarios, logistic issues may impede the ability to use the inhalational anesthetic agents in the pediatric ICU setting. Although operating rooms are designed or equipped for the delivery of inhalational anesthetic agents, the pediatric ICU may not be. Problems of administering these agents outside of the operating room including delivery and scavenging have led some authorities to recommend that patients requiring such therapy may be best cared for in the operating or recovery room setting (Bierman et al. 1986). Given the cost and logistics of such a practice, techniques have been developed for the administration of the inhalational anesthetic agents in the ICU setting. In addition to the technical and equipment requirements for delivering and scavenging these agents, as these agents are considered general anesthetics, hospital and state physician and nursing regulations may restrict those who are allowed to administer, monitor, and even adjust the inspired concentration of inhalational anesthetic agents whether they are administered in

the operating room or ICU environment. Such requirements may significantly increase the manpower issues and the costs if there are requirements that only anesthesia providers are allowed to administer inhalational anesthetic agents.

31.5.1 Delivery Techniques

As moving a patient to the OR is unlikely to be the answer to the logistic problems, in the majority of reports from the literature, the needed equipment was moved to the ICU setting. In many of the cases reported in the literature, a standard anesthesia machine and ventilator were brought from the OR to the ICU. Although the use of an OR anesthesia machine provides a quick and effective way of delivering the potent inhalational anesthetic agent, OR ventilators generally do not have the capabilities and ventilation options that are present on today's standard ICU ventilators. Although the ventilators on modern-day anesthesia machines allow options such as pressure- or volume-limited ventilation, alterations in the inspiratory time, the delivery of effective positive end expiratory pressure (PEEP), and even pressure-supported modes, newer modes of ventilation such as pressure-regulated, volume-controlled ventilation (PRVC) and changes in the inspiratory flow pattern are not available. Likewise, the alarm systems and monitoring capabilities of OR ventilators may not be equivalent to what is available on ICU ventilators.

A hybrid answer in some centers has been to use the Servo 900D anesthesia machine, which, although manufactured to be used in the operating room setting, has similarities to the Servo 900C ICU ventilator. On the Servo 900D anesthesia machine/ventilator, the vaporizer is positioned immediately distal from the air/oxygen blender prior to the working circuitry of the ventilator. Therefore, it allows the delivery of a set concentration of the inhalational anesthetic agent regardless of changes in ventilatory parameters. However, like many other ventilators that have been manufactured for use in the operating room, the Servo 900D has limited ventilator capabilities. It provides only volume-limited ventilation

with the tidal volume calculated by setting the minute ventilation and the respiratory rate.

Given the limitations of OR anesthesia machine ventilators and the familiarity of ICU physicians with standard ICU ventilators, options have been developed which may allow the administration of the inhalational anesthetic agents with standard ICU ventilators. One such option reported in the literature is the use of draw-over vaporizers positioned in the inspiratory limb of the ICU ventilator. In emergency situations or areas where pressurized gases are not available, these draw-over vaporizers have been used. These vaporizers add the inhalational anesthetic agent to the gas (generally air) which is drawn through the vaporizer by the patient's own spontaneous inspiratory effort. McIndoe et al. evaluated the efficacy of two draw-over vaporizers (The Ohmeda TEC, Ohmeda, UK and the Oxford Miniature Vaporizer, Penlon Ltd, UK) which were placed in the inspiratory limb of the ventilator circuit (McIndoe et al. 1997). The Ohmeda TEC delivered a predictable concentration only when the PIP was 20 cmH₂O. A higher PIP resulted in a delivered concentration which was greater than the set value. At a PIP of 60 cmH₂O, the error was greater than 200 %. The Oxford Miniature Vaporizer remained unaffected by alterations in the PIP. There was a tendency to deliver higher than set concentrations at the 2 % setting; however, none of the recorded inspiratory concentrations were more than 30 % greater than the set value. The authors concluded that at all tidal volumes, inspiratory pressures, and set inspired concentrations, the Oxford Miniature Vaporizer performed in a predictable fashion while the Ohmeda TEC vaporizer did not.

A second method for the delivery of the inhalational anesthetic agents in the ICU setting is to add flow from the vaporizer into the inspiratory limb of the ventilator circuit. An air-oxygen blender and vaporizer which are separate from the ICU ventilator are needed. The output from the vaporizer is added to the inspiratory limb of the ventilator circuit using a Y-piece attachment. A similar setup has been used in some studies and centers for the delivery of CO₂ into the inspiratory limb to maintain hypercarbia

in patients with single ventricle physiology (Kofke et al. 1985). However, depending on the flow rate from the vaporizer and the mode of ventilation, the added flow is likely to alter the delivered tidal volumes or PIP. In spontaneously breathing patients, the inspired concentration of the potent inhalational anesthetic agent will be affected by changes in minute ventilation.

Given these concerns, other centers have chosen to use a Servo 900C ventilator. For this purpose, there are two options reported in the literature. A Servo 900C can be fitted in the same manner as a Servo 900D with an anesthetic vaporizer (Tobias and Miltenberg 2009). With this setup, the gas flow from the air/oxygen blender passes through the vaporizer and then into the ventilator circuitry as it does for the Servo 900D operating room anesthesia machine and ventilator. With this setup, changes in ventilatory mode or tidal volume will not change the inspired concentration of the inhalational anesthetic agent. Alternatively, the gas flow from the vaporizer of a standard anesthesia machine can be connected using a piece of tubing into the low pressure inlet, which is located on the side of the Servo 900C ventilator (Fig. 31.3). This technique allows the use of the versatile settings for ICU ventilation of the Servo 900C ventilator and prevents alterations in tidal volume or airway pressures since the extra gas flow is delivered before the working circuitry of the ventilator. The major drawback of this technique is that since the agent is added to the gas flow of the ventilator, alterations in the minute ventilation will affect the inspired concentration of the inhalational anesthetic agent. An additional problem with the currently available techniques and devices is that the fresh gas flow requirements are high, and therefore there is significant consumption of the inhalational anesthetic agent, thereby increasing the cost of this therapy.

Given the problems with the currently available means of delivering the inhalational anesthetic agents in the pediatric ICU setting, novel devices or techniques for the delivery of these agents appear to be necessary. In attempt to overcome these issues and facilitate the delivery of inhalational anesthetic agents in the ICU setting,

Fig. 31.3 For the delivery of inhalational anesthetic agents during mechanical ventilation, the gas flow from a standard anesthesia machine can be added into low pressure inlet (arrow) on the side of the Servo 900C ventilator

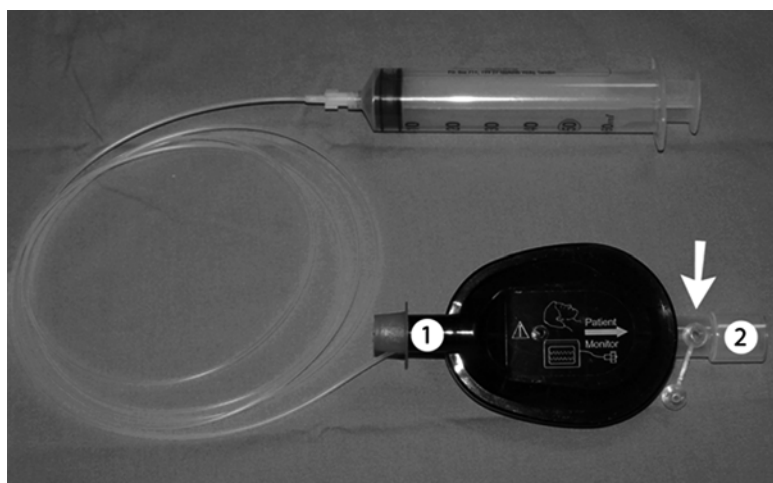
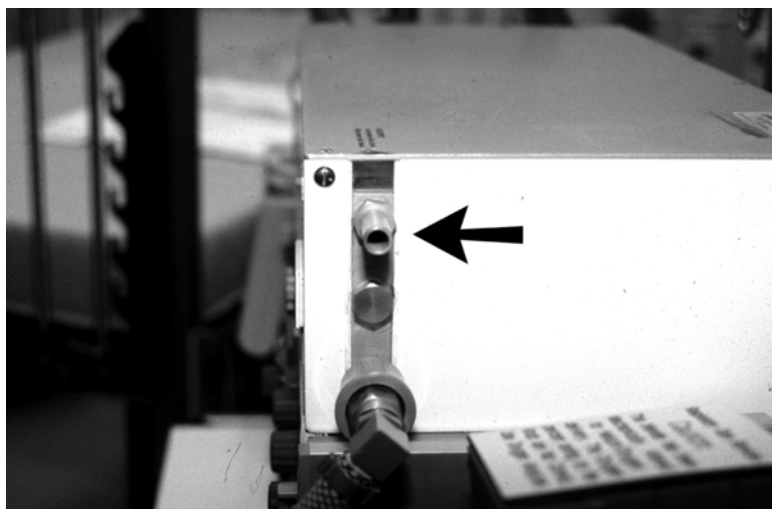


Fig. 31.4 The Anesthetic Conserving Device (AnaConDa® or ACD, Hudson RCI, Upplands Väsby, Sweden) was developed. The device is connected to the tubing from a standard ICU ventilator at point 1 and an endotracheal tube at point 2. There is a port just proximal

to the site of attachment to the endotracheal tube for gas sampling and monitoring the inspired concentration of the inhalational anesthetic agent (arrow). Any of the inhalational anesthetic agents can be infused into the device via the tubing using a standard infusion pump

the Anesthetic Conserving Device (AnaConDa® or ACD, Hudson RCI, Upplands Väsby, Sweden) was developed (Fig. 31.4). The ACD is a modified heat-moisture exchanger with a dead space of approximately 100 mL which provides a simplified means of administering the potent inhalational anesthetic agents in the ICU setting. The device is placed between the Y-piece of the ventilator circuit and the endotracheal tube (ETT). There is a port on the device just near its

attachment to the ETT which allows gas sampling and monitoring of the inspired concentration of the inhalational anesthetic agent. The device is nonspecific and can be used to vaporize and deliver any of the inhalational anesthetic agent. The inhalational anesthetic agents are drawn up into a syringe, which is included with the device, and infused onto the evaporator rod within the device via a syringe pump. As the inhaled gas passes from the ventilator and

through the device into the patient, the inhalational anesthetic agent is delivered. The desired inspired concentration is titrated by adjusting the infusion rate on the syringe pump based on the manufacturer's recommendations. The device also serves to scavenge the exhaled inhalational anesthetic agent. During exhalation, the inhalational anesthetic agent is adsorbed to the lipophilic carbon particle filter in the device and redelivered to the patient with subsequent breaths.

Preliminary trials in the adult population have demonstrated the efficacy of the device when used for the sedation of adult ICU patients during mechanical ventilation (Enluynd et al. 2002; Tempia et al. 2003). However, despite these successes, a bench and clinical study evaluating the device raised potential issues with the ACD which may warrant further evaluation (Berton et al. 2007). Using the ACD with a lung-analogue model, changes in anesthetic output were determined with changes in the infusion rate of the inhalational anesthetic agent (isoflurane) and changes in ventilatory parameters. There was a linear relationship between the isoflurane infusion rate and the delivered anesthetic concentration when the ventilator parameters were held constant. Although no change in the inspired concentration of the inhalational anesthetic agent was noted with alterations in PEEP and inspiratory times, a change in the tidal volume was identified as the single most important parameter affecting output from the ACD. Increasing the respiratory rate while holding the minute ventilation constant (decreasing tidal volume) resulted in an increased concentration of the agent while increasing the tidal volume without changing the respiratory rate resulted in decreased output. With clinical use, the authors also noted alterations in the delivered concentration based on alterations in the fresh gas flow from the ventilator. Other potential safety issues identified by the authors included an increase in the delivered concentration related to gravity-induced flow of the anesthetic agent during syringe changes when the syringe was disconnected 30 cm above the filter while a reverse flow effect decreased the inspired concentration when the disconnection was performed 30 cm below the filter. There has

also been concern expressed that the Luer-Lock fitted agent infusion line is the same as that used for standard intravenous tubing and could potentially result in the devastating complication of attachment of the inhalational anesthetic agent to an intravenous infusion site.

In a prospective evaluation of the efficacy of the ACD, 40 adult patients requiring sedation during mechanical ventilation were randomized to sedation with isoflurane administered with the ACD or a continuous infusion of midazolam (Sackey et al. 2004). The inspired concentration of isoflurane concentration was started at 0.5 % (infusion rate on the syringe pump of 1–3.5 mL/h according to the manufacturer's recommendations), while midazolam was infused at 0.02–0.05 mg/kg/h. The infusion rates of both agents were adjusted as needed and intravenous opioids administered for supplemental sedation and analgesia. There was no difference between the two groups in the percentage of time within the desired level of sedation (54 % with isoflurane and 59 % with midazolam), the need for supplemental opioids, or the use of bolus doses of sedative agents. Time to extubation (10 ± 5 versus 252 ± 271 min) and time to follow verbal commands (10 ± 8 versus 110 ± 132 min) were shorter with isoflurane than with midazolam. There were no differences in the hemodynamic parameters, urine volumes, and creatinine clearance between the two groups. The inorganic fluoride concentration was greater than 50 $\mu\text{mol/L}$ in 3 of the 20 patients (maximum value of 64 $\mu\text{mol/L}$) who received isoflurane using the ACD. Two adverse effects occurred with the ACD. One patient developed an increased end-tidal concentration of isoflurane after changing the ACD. The ACD was removed from the ventilator circuit, the end-tidal concentration decreased to the desired level, and the isoflurane delivery using the ACD was resumed. During the event, a transient decrease in BP which did not require therapy occurred. In another patient, an increased infusion requirement to maintain the desired concentration of isoflurane was noted. The ACD was changed earlier than per protocol (daily) and the infusion rate to achieve the desired inspired concentration returned to normal. Although there was no

change in resistance or compliance of the respiratory system, the authors speculated that copious secretions from the patient had nearly occluded the evaporator rod of the ACD.

Anecdotal experience with the ACD has been reported in three pediatric-aged patients (Sackey et al. 2005b). In two patients who required sedation during mechanical ventilation, effective sedation was achieved with an isoflurane concentration of 0.3–0.4 %, while 0.9 % isoflurane was required to control status epilepticus in the third patient. In two of the patients who weighed 30 and 40 kg, respectively, the ACD was placed distal to the Y-piece as has been described in the adult population. In a patient who weighed 20 kg, when the ACD was placed in this position, the patient became tachypneic with an increase in his respiratory rate from 25 to 35 breaths per minute. Although several ventilatory changes were attempted to compensate for the dead space added by the ACD, effective ventilation could not be achieved. The ACD was removed and placed into the inspiratory limb of the ventilator circuit. This allowed effective ventilation as well as delivery of isoflurane; however, the authors commented that by using the ACD in this position, there would be a loss of the rebreathing function of the device and no conservation of isoflurane usage. Based on this experience, the authors cautioned against the use of this device distal to the Y-piece in patients less than 30 kg unless a smaller model becomes available.

31.5.2 Environmental Pollution and Scavenging

Given the potential for adverse effects on cognitive function or health, the residual environmental or ambient concentrations of inhalational anesthetic agents should be minimized. The guidelines of the American Society of Anesthesiologists suggest that the ambient level of the inhalational anesthetic agent should be less than 2 ppm when used alone and less than 0.5 ppm when used in conjunction with N₂O. In Sweden, the recommended guidelines are for levels less than 10 ppm for long-term exposure and less than 20 ppm for

short-term exposure, while the UK recommends levels less than 50 ppm for long-term exposure (Vaughan et al. 1973). Although these levels have been shown to have no effect on cognitive function or behavior, there are no data regarding the potential adverse effects on health issues related to the chronic exposure to low levels of the inhalational anesthetic agents.

In the operating room setting, the exhaled gases from the anesthesia machine and ventilator are collected (scavenged) and evacuated. However, such devices and techniques may not be readily available on ICU ventilators and in the ICU setting. To deal with issues of scavenging, some centers have constructed specific rooms in the ICU with central scavenging systems similar to what is available in the operating room. However, such redesign and construction may be costly and therefore not feasible in most centers. Given the potential healthcare issues related to exposure to the inhalational anesthetic agents, a method to limit environmental pollution is necessary when these agents are administered outside of the OR setting. In the study of Sackey et al. (Sackey et al. 2005a), although environmental pollution when using the ACD to deliver the inhalational anesthetic agents was minimal and within the recommended limits in Sweden and the UK, there were periods of time when the ambient concentration of isoflurane exceeded the limits recommended in the USA, thereby suggesting that even when the ACD is used, scavenging may be required. Sackey et al. evaluated isoflurane consumption and environmental pollution in a prospective evaluation of 15 adult patients sedated with the ACD (Berton et al. 2007). In ten of the patients, there was active scavenging of the exhaled gas from the ventilator while no scavenging was performed in the other five patients. During use of the ACD and isoflurane administration, continuous monitoring of the ambient isoflurane concentration was performed using spectrophotometry in the 15 patients. Ambient isoflurane concentrations were well below internationally recommended peak, long-term exposure limits. The mean ambient isoflurane concentration was 0.1 ± 0.2 ppm with a maximum value of 0.5 ppm. Peaks of the ambient isoflurane concentration were short-lived, or low

amplitude, and infrequent. During the study period, there were only two episodes when the ambient isoflurane concentration was greater than 2 ppm for more than 10 min and two episodes when the concentration was greater than 5 ppm for greater than 1 min. Isoflurane requirements averaged 2.1 ± 1.0 mL/h, approximately 1/4th that previously reported and predicted with the administration of isoflurane from a vaporizer in the ICU setting.

In general, ICU ventilators are not routinely equipped to scavenge exhaled gases as the exhaled breath is vented to the environment. Therefore, some modification of the current design is required to avoid environmental pollution such as use of a device which adsorbs the exhaled inhalational anesthetic agent or connection of the exhalation port of the ventilator to a suction apparatus. Many of these devices absorb the inhalational anesthetic agent by using filters that contain activated charcoal. These devices were used most commonly in the operating room setting prior to the availability of effective central scavenging systems. There are various commercially available devices which contain activated charcoal to absorb the exhaled agent such as the Aldasorber (Cardiff Aldasorber, Chartan Aldred, Workshop UK). These devices can be modified to fit the exhalation port of the ventilator. Alternatively, tubing can be connected from the exhalation port of the ventilator to the central suction system. Johnston et al. suggested connecting the exhaust port of the ventilator to a t-piece that is attached to a 3-l self-inflating anesthesia bag (Johnston et al. 1990). Wall suction is then applied to the other end of the t-piece and adjusted so that the 3-l bag partially fills with each breath. Other authors have suggested surrounding the exhalation port with a semirigid container which is then connected to the wall suction. Regardless of the device used, obstruction to the exhalation port must be avoided as inadvertent PEEP and barotrauma may occur if there is obstruction to emptying of the ventilator. Evaluations of ICU contamination during the administration of isoflurane for sedation have failed to demonstrate environmental pollution with the implementation of such scavenging

systems (Hoerauf et al. 1995; Coleman et al. 1994).

Environmental pollution may also occur when the patient is disconnected from the ventilator for nursing care including suctioning. To eliminate such issues, some type of closed suctioning apparatus can be used to avoid the need to disconnect the patient from the ventilator. Alternatively, a bronchoscopy adaptor can be placed between the end of the endotracheal tube and the ventilator circuit to allow access for suctioning without the need to disconnect the patient from the ventilator (Hughes et al. 1992). As ongoing exhalation of the inhalational anesthetic agent may continue for hours following their use, it may be prudent to continue scavenging for 2–4 h following discontinuation of these agents.

31.5.3 Monitoring During the Delivery of Inhalational Anesthesia

In addition to the standard ICU monitoring of physiologic function during critical illness, additional equipment for the monitoring of the inspired and expired concentration of the inhalational anesthetic agent is also required. These devices, which use infrared techniques to determine the inspired and expired concentrations of the inhalational anesthetic agent, are routinely used in the operating room. In addition to providing the inhaled and exhaled concentration of the inhalational anesthetic agent, they also measure inspired oxygen concentration and end-tidal carbon dioxide. Such monitoring is especially important when delivery techniques are used in which the vaporizer setting does not equal the inspired concentration delivered. This may occur when the vaporizer output is added to the inspiratory limb or the low pressure inlet of the Servo 900C ventilator. In these cases, the concentration setting on the vaporizer will not equal the delivered concentration. Additionally, changes in minute ventilation will change the inspired concentration of the inhalational anesthetic agent. When the ACD is used, the concentration is adjusted by changing the infusion rate of the inhalational

anesthetic agent. In all of these cases, additional monitoring is needed to accurately measure the inspired and expired concentration of the inhalational anesthetic agent. These monitoring devices are routinely available in all operating rooms and are compact enough that they can easily be moved into the ICU setting.

31.6 Summary

The inhalational anesthetic agents are used on a daily basis to provide intraoperative anesthesia. These agents provide the required requisites of general anesthesia including amnesia, analgesia, control of the sympathetic nervous system, and skeletal muscle relaxation. Although the physiologic effects differ depending on the agent, general effects include a dose-related depression of ventilatory and cardiovascular function. With increasing anesthetic depth, there is a progressive decrease in alveolar ventilation with a reduction in tidal volume and an increase in PaCO_2 in spontaneously breathing patients. These agents also decrease MAP in a dose-dependent fashion. Their effects on myocardial contractility and systemic vascular resistance vary depending on the agent with halothane depressing myocardial contractility and desflurane and isoflurane decreasing systemic vascular resistance. The central nervous system effects include nonspecific cerebral vasodilatation which may increase intracranial pressure (ICP) in patients with compromised intracranial compliance. Secondary effects on end-organ function may result from the metabolism of these agents and the release of inorganic fluoride. However, in the majority of patients, the end-organ effects are well tolerated, and given their beneficial physiologic effects (sedation, analgesia, bronchodilatation, anticonvulsant properties, and neuroprotection, the latter being controversial), there may be a role for these agents in the ICU setting not only for sedation but also as therapeutic agents in the treatment of status asthmaticus and status epilepticus.

When used for sedation during mechanical ventilation, the literature suggests that the potent inhalational anesthetic agents are more

efficacious than intravenous agents such as midazolam as well as providing a more rapid awakening. Isoflurane remains the agent used most commonly for ICU sedation and other therapeutic interventions given its limited metabolism (limited fluoride and TFA production), limited end-organ toxicity profile, and cost when compared with the other available agents. As with any agent used for prolonged sedation in the ICU setting, tolerance may develop, and withdrawal phenomena have been reported following prolonged administration.

In addition to their use for sedation, these agents have also been shown to be effective in the treatment of status asthmaticus and status epilepticus which is refractory to conventional therapy. In the pediatric population, experience with these agents in these settings is anecdotal consisting mostly of isolated case reports and case series.

Factors impeding the use of these agents outside of the operating room are issues regarding delivery, monitoring, and scavenging. As outlined above, there are several options for the delivery in the ICU setting including the use of a standard anesthesia machine including the Servo 900D, modification of an ICU ventilator with the addition of a vaporizer, addition of the agent to inspiratory limb of the ventilator circuit, or the ACD. Scavenging of exhaled gases is needed to avoid environmental pollution. Additional monitoring is also required to measure the inspired and expired concentrations during the use of the inhalational anesthetic agents. With such caveats in mind, the inhalational anesthetic agents may have a role for the provision of the sedation during mechanical ventilation as well as therapeutic agents to treat refractory status asthmaticus and epilepticus.

Essentials to Remember

- There remain several beneficial effects of the inhalational anesthetic agents which may make these useful in the pediatric ICU setting including their ability to provide sedation, their

anticonvulsant properties, and their bronchodilatory effects on the airways.

- When the inhalational anesthetic agents are used in the pediatric ICU patient, the adverse effect of greatest clinical concern is the potential for their effects on hemodynamic function especially in the patient with comorbid cardiac disease or when these agents are used in high concentrations.
- The major obstacle to the use of the potential inhalational agents in the pediatric ICU setting is their delivery through standard ICU ventilators and the need to scavenge the exhaled gases to prevent environmental pollution.

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32.1 In Neonatal Respiratory Failure

Praveen Kumar

Educational Aims

- To review the use of various pharmacologic agents in the prevention and treatment of neonatal respiratory disease
- To specifically discuss the evidence for use of two most cost-effective interventions in neonatal medicine – antenatal steroids and surfactant replacement therapy
- To discuss the role of inhaled nitric oxide and other cheaper alternatives like sildenafil, magnesium sulphate and adenosine in the management of pulmonary hypertension of the newborn
- To review the status of various drugs for chronic lung disease
- To dissect the role of the above strategies in low-resource settings

The survival rates of neonates suffering from respiratory failure have improved tremendously over the last three decades. This has occurred because of general improvements in the neonatal intensive care as well as widespread use of invasive and non-invasive respiratory support. Numerous technological advances have given us newer and far better ventilators as compared to a decade ago. However, the rates of chronic lung disease (CLD) have not decreased. It is realised that although CLD has a multifactorial pathogenesis, the single most important factor responsible for occurrence of CLD is probably the endotracheal tube. Hence, all efforts are made either to avoid intubation or to minimise the duration of intubation by taking help of many adjunctive therapies. However, many of these therapies, though used very commonly, are not based on strong evidence.

32.1.1 Antenatal Steroids

Though antenatal steroids are more of a preventive medicine, they need to be mentioned here because they are the most cost-effective intervention which can decrease the incidence and severity of respiratory distress syndrome (RDS) and hence its complications. In spite of this fact, use of antenatal steroids is not a routine practice in many developing countries and is suboptimally

practised even in developed countries. The pre-natal steroid use thus remains a case of missed opportunity. If fully scaled up, this intervention could save up to 500,000 neonatal lives annually (Mwansa-Kambafwile et al. 2010). Administration of antenatal corticosteroids to pregnant women at risk for premature delivery is associated with an overall reduction in neonatal death, RDS, intraventricular haemorrhage (IVH), necrotising enterocolitis (NEC), need for respiratory support, intensive care admissions and systemic infections in the first 48 h of life in a wide range of gestational ages from 26 to 34^{6/7} weeks (Roberts and Dalziel 2006). Some guidelines recommend considering the use of antenatal steroids after 34 weeks' gestation also if there is evidence of pulmonary immaturity (Committee on Obstetric Practice 2002; RCOG 1996; U.S. Department of Health and Human Services and Public Health 1994). The overall reduction in neonatal mortality with the use of antenatal steroids is to the tune of 60–69 % (Crowley et al. 1990; Doyle et al. 1986) and that of IVH by about 50 % (RCOG 1996). Others have reported reduction in the incidence of PDA (Papageogiou et al. 1989; National Institute of Health 1994). One study had shown a reduction in the incidence of CLD from 35 to 25 % with the use of antenatal steroids (Van Marter et al. 1990), but this has not been replicated by others. There is a potential benefit commencing within hours of the first dose. After one course (total of 24 mg of betamethasone or dexamethasone given over 48 h) of antenatal steroids, the maximum benefits are seen if the fetus is delivered 24 h after and within 7 days of the last dose (National Institute of Health 1994). However, use of antenatal steroids reduces neonatal deaths even when infants are born <24 h after the first dose (Roberts and Dalziel 2006). Another study has confirmed that incomplete courses of antenatal steroids are also beneficial (Elimian et al. 2003). It has also been shown that improved neonatal outcomes continue even beyond 7 days of the last dose (Goldenberg and Wright 2001). The choice is between betamethasone (12 mg intramuscularly every 24 h for 2 doses) and dexamethasone (6 mg intramuscu-

larly every 12 h for 4 doses). Both betamethasone and dexamethasone are identical in biologic activity, readily cross the placenta, are devoid of mineralocorticoid activity, cause relatively weak immunosuppression and have longer duration of action (Ohrlander et al. 1975; Osathanondh et al. 1977). However, recent trials have shown betamethasone is associated with a greater reduction in risk of death than dexamethasone, corroborating Jobe's results in 2004 (Lee et al. 2006; Jobe and Soll 2004). Two other studies have indicated a decreased risk of cystic periventricular leukomalacia (PVL) in premature infants exposed to betamethasone, whereas this association was not found with dexamethasone (Baud et al. 1999; Spinillo et al. 2004).

Frank chorioamnionitis is usually considered a contraindication to the use of antenatal steroids. A recent review and meta-analysis, however, found encouraging results (Been et al. 2011). Seven observational studies were included in this review. In histological chorioamnionitis (5 studies), antenatal steroids were associated with reduced mortality (OR 0.45; 95 % CI 0.30–0.68; $P=0.0001$), RDS (OR 0.53; 95 % CI 0.40–0.71; $P<0.0001$), PDA (OR 0.56; 95 % CI 0.37–0.85; $P=0.007$), IVH (OR 0.35; 95 % CI 0.18–0.66; $P=0.001$) and severe IVH (OR 0.39; 95 % CI 0.19–0.82; $P=0.01$). In clinical chorioamnionitis (4 studies), antenatal steroids were associated with reduced severe IVH (OR 0.29; 95 % CI 0.10–0.89; $P=0.03$) and PVL (OR 0.35; 95 % CI 0.14–0.85; $P=0.02$). It was concluded that antenatal steroids may be safe and reduce adverse neonatal outcome after preterm birth associated with chorioamnionitis. There is a need for randomised clinical trials to address this issue.

In the situation of PIH and diabetes, all fetuses at risk of being delivered preterm should be offered the benefits of a single course of antenatal steroids. Several large trials (Crowther et al. 2006; Guinn et al. 2001; Murphy et al. 2008; TEAMS Trial; Wapner et al. 2006) have been developed in recent years comparing single versus multiple courses. The benefits of repetitive courses of corticosteroids may be real, but they seem to be modest relative to the potential for adverse outcomes. A Cochrane review on repeat

doses of prenatal corticosteroids concluded that 'Repeat dose(s) of prenatal corticosteroids reduce the occurrence and severity of neonatal lung disease and the risk of serious health problems in the first few weeks of life. These short-term benefits for babies support the use of repeat dose(s) of prenatal corticosteroids for women at risk of preterm birth. However, these benefits are associated with a reduction in some measures of weight, and head circumference at birth, and there is still insufficient evidence on the longer-term benefits and risks' (Crowther and Harding 2007). Similar conclusions were reported by a recent review (Bevilacqua et al. 2010).

In low-resource settings, the cost of surfactant still remains very high and unaffordable for most patients. In sharp contrast, antenatal steroids are very cheap as well as effective in preventing RDS. Use of antenatal corticosteroids has benefits beyond their effects on the fetal lung. Preterm infants exposed to antenatal steroids have better transition at birth, higher blood pressures, better renal function and decreased risk of IVH and NEC. Further, antenatal corticosteroids act synergistically with surfactant treatment to improve outcomes – better responses to surfactant therapy, including improved compliance, better gas exchange and less lung injury with ventilation. Several studies have found that either treatment was better than no treatment, and both treatments acted synergistically (Farrell et al. 1989).

32.1.2 Surfactant Replacement Therapy

Surfactant is a mixture of phospholipids, neutral lipids and specific proteins and is synthesised and secreted by type II epithelial cells. The main function of surfactant is to reduce surface tension and prevent alveolar atelectasis. Phospholipids are responsible primarily for the surface tension-lowering activity, but other low molecular weight surfactant proteins (SPs) like the hydrophobic SP-B and SP-C enhance the biophysical activity of phospholipids (Whitsett and Weaver 2002). Three kinds of surfactants are generally available: animal-derived surfactants (natural surfactants), which are extracted from either minced

lungs or lung lavage and have high phospholipid concentration and contain the proteins SP-B and SP-C; first-generation synthetic surfactants (artificial surfactant), which do not have surfactant proteins; and newer synthetic surfactants – containing recombinant surfactant proteins or synthetic peptides whose structure and properties resemble that of SP-B or SP-C (Ghodrat 2006). Three approaches have been used to administer surfactant: prophylactic (treatment within the first minutes after birth, usually by 15–30 min, before onset of respiratory symptoms), early rescue (treatment within 2 h, when signs of respiratory distress are present) or late rescue (treatment after 2 h).

Surfactant replacement therapy (SRT) for RDS is a major breakthrough in neonatal medicine that has revolutionised the survival of premature infants with RDS over the last two decades (Fujii and Carillo 2009). It is one of the most well-studied therapies in newborns; more than 40 trials have enrolled almost 10,000 infants and demonstrated a consistent and impressive reduction in neonatal mortality, considering all types of surfactants and all types of approaches (Halliday 2005). Surfactant decreases the need for ventilatory support and complications such as air leaks and improves survival in infants with RDS between 24 and 34 weeks' gestation (Engle 2008; Soll and Ozek 2010; Seger and Soll 2009). The effect is significantly greater in infants less than 30 weeks' gestation with birth weight <1,250 g. Because the increase in survival is observed mainly among extremely premature infants, the incidence of CLD has not reduced dramatically despite the widespread use of surfactant. Numerous Cochrane reviews are available looking at various aspects of surfactant therapy – prophylactic use of protein-free synthetic surfactants or animal surfactants, rescue use of surfactants, multiple versus single dose of surfactant, etc. Prophylactic administration of protein-free synthetic surfactants resulted in a decrease in the risk of pneumothorax (RR 0.67, 95 % CI 0.50, 0.90), pulmonary interstitial emphysema (RR 0.68, 95 % CI 0.50, 0.93) and neonatal mortality (RR 0.70, 95 % CI 0.58, 0.85). No differences were seen in the risk of IVH, NEC, BPD, ROP

and cerebral palsy. There was an increase in the risk of PDA (RR 1.11, 95 % CI 1.00, 1.22) and an increase in the risk of pulmonary haemorrhage (RR 3.28, 95 % CI 1.50, 7.16) (Soll and Ozek 2010). A review of 13 randomised controlled trials of treatment of established RDS with animal-derived surfactant showed a significant decrease in the risk of any air leak (RR 0.47, 95 % CI 0.39, 0.58), pneumothorax (RR 0.42, 95 % CI 0.34, 0.52), pulmonary interstitial emphysema (RR 0.45, 95 % CI 0.37, 0.55), neonatal mortality (RR 0.68, 95 % CI 0.57, 0.82), risk of mortality prior to hospital discharge (RR 0.63, 95 % CI 0.44, 0.90) and BPD or death at 28 days of age (RR 0.83, 95 % CI 0.77, 0.90). No differences are reported in the risk of PDA, NEC, IVH, BPD or ROP (Seger and Soll 2009). An updated Cochrane systematic review of prophylactic vs selective surfactant was published in 2012 (Rojas-Reyes et al. 2012). The combined overall results did not show any benefit of prophylactic surfactant. A meta-analysis of studies conducted in 1990s when routine early application of CPAP was not practiced revealed decrease in mortality and incidence of air leaks. However, a meta-analysis of two recent large trials in an era of high antenatal steroid use and which applied routine early CPAP found a trend towards increased mortality or CLD with the use of prophylactic surfactant. In general, earlier administration of surfactant results in improved outcomes. OSIRIS trial reported a drop in mortality by 16 % if the time to give surfactant was reduced from 3 to 2 h (The OSIRIS Collaborative Group 1992). One method to reduce the time lag in administering surfactant is to use 'click test' (Osborn et al. 2000). Use of the click test in ventilated infants of <28 weeks' gestation resulted in a 39 % reduction in use of surfactant compared with rescue therapy based on clinical and early chest radiograph diagnoses of RDS. Several large clinical trials have demonstrated that early rescue surfactant therapy also significantly improves survival and reduces complications in RDS and is highly cost-effective. The meta-analysis of 2 trials of multiple- versus single-dose animal-derived surfactants in infants with established RDS suggests a reduction in the risk of pneumothorax (RR 0.51, 95 % CI 0.30, 0.88) and a trend toward a reduc-

tion in the risk of mortality (RR 0.63, 95 % CI 0.39, 1.02). One study of multiple- versus single-dose synthetic surfactant in infants at high risk of RDS reported a decrease in NEC (RR 0.20, 95 % CI 0.08, 0.51) and mortality (RR 0.56, 95 % CI 0.39, 0.81). No data on long-term neurological or pulmonary outcome were reported. No complications associated with multiple-dose treatment were reported in the identified trials. The authors concluded that the ability to give multiple doses of surfactant to infants with ongoing respiratory insufficiency leads to improved clinical outcome and appears to be the most effective treatment policy (Soll and Ozek 2009).

In summary, synthetic surfactants without surfactant proteins are inferior to animal-derived surfactant preparations. The data regarding the relative efficacy of the various animal-derived surfactants is limited, but there is a trend favouring surfactant preparations with higher concentrations of phospholipids and surfactant proteins. A higher initial dose of phospholipids may also be important, especially for preterm infants less than 32 weeks of gestation (Fujii and Carillo 2009).

Majority of infants who receive surfactant may be manageable on CPAP, and surfactant may be administered by INSURE technique (*IN*tubate, give *SUR*factant and *Ext*tubate to CPAP within 3–5 min) (Stevens et al. 2007). Another similar study reported success with INSURE in babies between 23 and 29 weeks with 60 % being managed with INSURE, 16 % NCPAP alone and only 24 % receiving MV (Dani et al. 2010). INSURE technique has the advantage of delivering surfactant into the lungs effectively, yet minimising the duration of intubation. However, even short duration of endotracheal intubation can initiate the inflammatory cascade leading to BPD. In addition, the risks and complications associated with pre-medication and intubation are well known. Therefore, minimally invasive or non-invasive methods of surfactant delivery like intrapartum pharyngeal instillation, laryngeal mask airway, feeding or vascular catheters and aerosolization are being explored (Lopez et al. 2013).

32.1.2.1 Comparison of Surfactants

At the present time, beractant (Survanta®), calfactant (Infasurf®) and poractant alpha

(Curosurf®) are the three commonly used natural surfactants worldwide. They are available in different concentrations and packing sizes. There are very few head-to-head comparisons between different surfactant preparations in the market. All of them work efficiently and there is little to choose between them. In the developing world, since the family has to purchase the surfactant, the choice of the surfactant is often determined by the weight of the baby and the packing sizes available so that the most economical one is used. Ramanathan et al. demonstrated that treatment with double dose of poractant alpha (200 mg/kg initial dose) resulted in rapid reduction in supplemental oxygen with the need of fewer additional doses of surfactant and significantly reduced mortality as compared to either beractant or poractant alpha (100 mg/kg dose) in infants ≤ 32 weeks' gestation with RDS (Ramanathan et al. 2004). Treatment with poractant (Curosurf) when compared to beractant (Survanta) was associated with faster weaning of supplemental oxygen, PIP and MAP during the first 24 h after treatment (Speer et al. 1995). In a meta-analysis of results, mortality was significantly lesser (OR 0.35, CI 0.13–0.92) with poractant alpha. The beneficial effects of poractant over beractant have also been reported in preterm infants ≤ 29 weeks in a recent study by Fujii et al. (2010). These differences in outcome may be due to differences in composition in terms of phospholipids, SP-B content, antioxidant phospholipids, plasmalogens and anti-inflammatory properties.

Newer synthetic surfactants such as lucinactant (Surfaxin®, Discovery Laboratories, USA) contain protein B mimic synthetic peptide, sinapultide. They can avoid the disadvantage of potential exposure to animal-borne infectious agents or animal proteins that could induce an immune response in fragile premature infants (Lal and Sinha 2008). Prophylactic use of lucinactant has been shown to be more effective than colfosceril (synthetic surfactant) in reducing the incidence of RDS (39 % vs. 47 %). However, there was no difference when compared to beractant (Survanta®). Sinha et al. reported that lucinactant and poractant alpha were similar in terms of efficacy and safety when used for the prevention and treatment of RDS among preterm infants

(Sinha et al. 2005). The Cochrane review on protein-containing synthetic surfactant versus animal-derived surfactant extract for the prevention and treatment of respiratory distress syndrome (two trials) reported no statistically significant clinical differences in death, other outcomes and CLD (Pfister et al. 2009).

It is known that even a short period of intubation can initiate the cascade of events leading to CLD. Yet, as of now, endotracheal tube is the standard route of administration of SRT. The superiority of endotracheal tube with side port for surfactant administration (without need for disconnection from ventilator) over direct instillation into the endotracheal tube is debatable. Other routes, like laryngeal mask airway (LMA), intra-amniotic instillation and nebulisation, are experimental at present (Trevisanuto et al. 2005; Mazela et al. 2007; Donn and Sinha 2008; Abdel-Latif et al. 2010).

Usually, surfactant should be administered in experienced intensive care units having the equipment and personnel to anticipate, recognise and treat complications. It is realised that surfactant therapy is only one part of the comprehensive care of premature infants. The importance of adequate infrastructure, asepsis and meticulous nursing care to optimise survival in surfactant-treated infants has always been stressed. However, SRT may have a role in level II units prior to transport to a specialised NICU. In Israel, very low birth weight outborn infants were shown to have an outcome comparable with that of inborn babies if adequate perinatal care including surfactant administration was provided prior to transportation to a tertiary centre (Arad et al. 2006). Others have shown longer hospital stay and longer duration of ventilation if surfactant was given pre-transport (Costakos and Allen 1996).

32.1.2.2 Status in Developing Countries

In the initial years, surfactant was very expensive and available only in the smuggled market in some developing countries resulting in very restricted use. With the licensing of surfactant import and increasing volumes of usage, the prices of surfactant have decreased by more than half over the last decade, and currently it may be priced lower than that in the developed countries.

However, since families themselves have to bear the cost in most situations, less than 50 % of the population may be able to afford it. In view of the huge needs, efforts are ongoing to manufacture the surfactant locally and reduce the costs by another two-thirds. The data from developing countries is however limited. Virtually all of the trials have been done in developed countries. It can be debated whether babies from developing countries who are more likely to be asphyxiated, malnourished and have concomitant infections would respond in similar manner as their counterparts from developed countries. A study by Narang A et al. showed that SRT reduced mortality in Indian babies and was cost-effective in terms of reducing duration of ventilation and hospital stay. It decreased morbidity as the incidence of sepsis and chronic lung disease was lower in babies who received surfactant (Narang et al. 2001). Similar experiences have been reported from Korea (Bae and Hahn 2009).

32.1.2.3 Expanding Use of Surfactant in Newborns

Apart from RDS, qualitative or quantitative deficits of surfactant are often involved in the pathogenesis of various respiratory disorders in late preterm and term babies, including meconium aspiration syndrome (MAS), pneumonia, congenital diaphragmatic hernia (CDH) and inherited disorders of surfactant metabolism involving mutations in the SP-B and SP-C genes (Lacaze-Masmonteil 2007; Whitsett 2006). Preterm infants who have or do not have initial RDS may also exhibit a secondary surfactant deficiency during the course of chronic lung disease or after an acute episode of lung injury such as aspiration, pulmonary haemorrhage or pneumonia. All these disorders may represent potential targets for surfactant therapy.

32.1.2.4 Meconium Aspiration Syndrome (MAS)

The pathophysiologic mechanisms of hypoxaemia in MAS include surfactant dysfunction or inactivation. The hydrophobic chloroform-soluble fraction of meconium is the most potent inhibitor of surfactant function in vitro and in

vivo in a dose-dependent fashion (Dargaville et al. 2001). The inhibiting effect of meconium on surfactant function can be overcome by increasing the concentration of surfactant. Synthetic surfactant preparations containing recombinant or analog peptides are more resistant to meconium in vitro than natural animal-derived surfactant (Herting et al. 2001). In animal models of MAS, bolus administration of surfactant is associated with an improvement in mechanical properties, gas exchange, lung inflammation and histology (Hilgendorff et al. 2006). Three randomised controlled trials have shown some benefits of the administration of several boluses of a natural surfactant in the treatment of MAS (Findlay et al. 1996; Lotze et al. 1998; Soll and Dargaville 2007; Chinese Collaborative Study Group for Neonatal Respiratory Diseases 2005). Although there was no difference in mortality in any of these trials, the administration of multiple doses of a natural surfactant was found to improve oxygenation in all, to reduce the need for extracorporeal membrane oxygenation (ECMO) in two and to reduce the risk of pneumothorax in one. In contrast to RDS treatment, where only one dose usually is sufficient to improve oxygenation and permit extubation, long-lasting improvement in oxygenation usually was seen only after at least the second bolus, supporting the need of repeated doses 6 h apart to overcome ongoing surfactant inactivation in infants who have MAS (Findlay et al. 1996; Lotze et al. 1998; Soll and Dargaville 2007). The need to titrate the ongoing inhibiting activity of meconium may account for the improved compliance observed after continuous infusion of surfactant over 1 h compared with bolus administration in a rabbit model of MAS (Robinson and Roberts 2002). In this respect, by removing meconium, inflammatory cells, oedema fluid and surfactant inhibitors from the alveolar space, bronchoalveolar lavage with dilute animal-derived or protein-containing artificial surfactant may be a promising approach for the treatment of severe MAS. This method was also evaluated in the treatment of severe MAS in an open and a small randomised controlled pilot study (Lam and Yeung 1999; Wiswell et al. 2002). In the

latter trial, 25 infants who had severe MAS were submitted to a series of bronchoalveolar lavages with dilute lucinactant. A trend toward a more rapid improvement in oxygenation and a shorter duration of mechanical ventilation was observed in the treated group. However, 20 % of the subjects had the procedure abandoned because of hypoxaemia or hypotension. Based on these results, phase 3 clinical trials have been initiated to assess the efficacy and the safety of bronchoalveolar lavage with dilute lucinactant or beractant in severe MAS. Although so far it has not been approved specifically for this disorder by any regulatory agency, surfactant therapy using bolus administration seems to be effective in the management of MAS. Since MAS can have varied pathophysiologic mechanisms of which surfactant deficiency is only one, an approach may be to judge the lung volume clinically or radiologically and use surfactant if the picture is like RDS. In the developing world, use of SRT for MAS may be a very expensive proposition in view of the bigger weight of these babies and the need for multiple doses. The optimal method of administration (lavage or bolus), preparation (natural or peptide-containing synthetic preparation), dosing and time in the course of the disease when surfactant should be given remain to be determined.

32.1.2.5 Late Preterm RDS

Most of the evidence for the benefit of surfactant has come from investigations performed in low or very low birth weight babies. Although RDS is rare in late preterm infants (34–36 weeks), it remains a concern because this population represents 75 % of all preterm births (Jain and Eaton 2006). Lack of clearance of lung fluid, relative surfactant deficiency and secondary inhibition of surfactant function are the major pathophysiologic mechanisms of respiratory distress in late preterm babies. No study has yet specifically evaluated the benefit of surfactant treatment in this population.

32.1.2.6 Pneumonia

In neonatal pneumonia, surfactant may be inactivated by plasma-derived proteins, blood components present in the alveolar spaces (haemoglobin,

fibrinogen and immunoglobulins) and by phospholipases released by bacteria. The alveolar epithelium responsible for the synthesis and secretion of surfactant may be injured. In a retrospective review of a large series of preterm and term infants who had respiratory failure associated with GBS sepsis, improved oxygenation and decreased ventilatory requirements were observed after administration of natural surfactant (Herting et al. 2000). SP-A and SP-D, two complex glycoproteins present in pulmonary surfactant, play a major role in the lung defence barrier against pathogenic organisms (Sano and Kuroki 2005). It is hypothesised that SP-A- or SP-D-enhanced surfactants might be beneficial in the treatment of pulmonary inflammation due to infectious diseases (Kingma and Whitsett 2006). The role of SRT in Gram-negative pneumonias has not been studied.

32.1.2.7 Pulmonary Haemorrhage

Haemoglobin and plasma proteins, such as fibrinogen, which are released in alveolar spaces after haemorrhage are powerful inhibitors of endogenous surfactant (Kobayashi et al. 1991). This process may be reversed by increasing the surfactant/inhibitor ratio in the alveolar spaces, like in case of MAS. The administration of an animal-derived surfactant in infants who have pulmonary haemorrhage has been shown to improve the oxygenation index and lung compliance in two uncontrolled reports (Pandit et al. 1995a; Amizura et al. 2003). Improvements generally were immediate and long-lasting. Treatment with exogenous surfactant may be a reasonable option in compromised infants who have severe pulmonary haemorrhage, and further trials are warranted.

32.1.2.8 Congenital Diaphragmatic Hernia (CDH)

In animal models of CDH, it has been shown that surfactant deficiency may be associated with pulmonary hypoplasia and pulmonary hypertension. Few controlled and small-sized studies suggested modest clinical improvement after surfactant administration (Glick et al. 1992). The only but small randomised trial of 17 patients published

thus far does not show clinical benefit (Lotze et al. 1994). Retrospective analyses of a large series of treated patients also fail to support any benefit for the use of surfactant therapy in term babies who have CDH (Lally et al. 2004; Van Meurs et al. 2004).

32.1.2.9 Chronic Lung Disease

Surfactant function and contents of SP-A, SP-B and SP-C are altered in mechanically ventilated very preterm babies who experience episodes of lung infection or deterioration. A significant but transient improvement in oxygenation after administration of beractant has been reported in a small number of babies who had stable chronic lung disease and were on mechanical ventilation (Pandit et al. 1995b). The role of intermittent repeated doses of surfactant during the course of chronic lung disease or specifically during episodes of respiratory decompensation needs investigation.

32.1.3 Pulmonary Vasodilators

32.1.3.1 Inhaled Nitric Oxide (iNO)

Numerous pulmonary vasodilators have been tried in the past to treat persistent pulmonary hypertension in the newborn (PPHN), but because of inconsistent effects and serious side effects, they are not used routinely. iNO, which is a potent selective pulmonary vasodilator, has been a great success in comprehensive multicentre trials. iNO along with assisted ventilation is currently the mainstay of therapy of PPHN in the developed world. A Cochrane meta-analysis found 14 eligible randomised controlled studies in term and near-term infants with hypoxia comparing iNO to control with or without backup treatment (Finer and Barrington 2006a). iNO improved outcome in hypoxaemic term and near-term infants by reducing the incidence of the combined endpoint of death or need for ECMO. The reduction was entirely due to a reduction in need for ECMO; mortality was not reduced. Oxygenation improved in approximately 50 % of infants receiving iNO. The oxygenation index decreased by a (weighted) mean of 15.1 within 30–60 min

after commencing therapy, and PaO₂ increased by a mean of 53 mmHg. The outcome of infants with diaphragmatic hernia was not improved; rather there was a suggestion that outcome was slightly worsened. The incidence of disability, incidence of deafness and infant development scores were similar between tested survivors who received nitric oxide or not. The authors concluded that it appears reasonable to use inhaled nitric oxide in an initial concentration of 20 ppm for term and near-term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia (Finer and Barrington 2006a). Another Cochrane review for use of iNO in preterms found 14 randomised controlled trials (Barrington and Finer 2010). The trials were grouped post hoc into three categories depending on the entry criteria: entry in the first 3 days of life based on oxygenation criteria, routine use in intubated preterm babies and later enrolment based on an increased risk of BPD. The usefulness of the overall analyses was considered limited by the differing characteristics of the studies, and only subgroup analyses were performed. Nine trials of early rescue treatment of infants based on oxygenation criteria demonstrated no significant effect of iNO on mortality or BPD. The subgroup of three studies with routine use of iNO in intubated preterm infants did not demonstrate significant reduction in the combined outcome of death or BPD (typical RR 0.93 (95 % CI 0.86, 1.01)). Later treatment with iNO based on the risk of BPD demonstrated no significant benefit for this outcome. There was no clear effect of iNO on the frequency of all grades of IVH or of severe IVH. Early rescue treatment was associated with a nonsignificant 20 % increase in severe IVH. No effect on the incidence of neurodevelopmental impairment was found. The authors concluded that iNO as rescue therapy for the very ill preterm infant does not appear to be effective. Early routine use of iNO in preterm infants with respiratory disease does not affect serious brain injury or improve survival without BPD. Later use of iNO to prevent BPD might be effective but requires further study. A recent systematic review found a 7 % reduction in the risk of the composite outcome of death or BPD at 36 weeks for preterm

infants treated with iNO compared with controls but no reduction in death alone or BPD and concluded that there is currently no evidence to support the use of iNO in preterm infants with respiratory failure outside the context of rigorously conducted randomised clinical trials (Donohue et al. 2011). The NIH Consensus Development Conference also stated that the combined evidence from the 14 randomised controlled trials of iNO treatment in premature infants of ≤ 34 weeks' gestation shows only equivocal effects on pulmonary outcomes, survival and neurodevelopmental outcomes (Cole et al. 2011).

All trials of iNO in term and preterm neonates have been conducted in the developed world. Not only the equipment is expensive, the continuing costs of medical grade iNO are even higher. Anecdotal experience has been reported from some centres (Goh et al. 2001).

32.1.3.2 Phosphodiesterase Inhibitors

Nitric oxide gas is very expensive and not easily available in most developing countries. In addition 30 % of patients of PPHN do not respond to iNO. Hence, there is an ongoing exploration for alternatives. High concentrations of phosphodiesterases in the pulmonary vasculature have led to the use of phosphodiesterase inhibitors such as sildenafil or milrinone. A Cochrane review identified two small eligible trials (Shah and Ohlsson 2007). The total number of enrolled patients in the two studies was 37. Both studies were performed in resource-limited settings where iNO and high-frequency ventilation are not available. Both studies reported statistically significant improvement in oxygenation (reduction in oxygenation index) in the sildenafil group. One study reported a strongly protective effect on mortality (RR 0.17, 95 % CI 0.03, 1.09) favouring the sildenafil group. However, this result needs to be replicated in larger studies. No clinically important side effects were reported. The authors concluded that the safety and effectiveness of sildenafil in the treatment of PPHN have not yet been established and its use should be restricted within the context of randomised controlled trials. However, since sildenafil is cheap and easily

available and can even be given orally, it is used very frequently in the developing world. A recent randomised controlled trial allocated 34 infants to MgSO₄ (RCOG 1996) and 31 infants to sildenafil group (Uslu et al. 2011). The time to reach the adequate clinical response (defined as oxygenation index (OI) of <15 , a pulmonary artery pressure of <20 mmHg), duration of mechanical ventilation and number of the patients requiring inotropic support were significantly lesser in the sildenafil group.

32.1.3.3 Other Drugs for PPHN

32.1.3.3.1 Magnesium Sulphate

Magnesium sulphate is very cheap and ubiquitously available. Apart from vasodilatory effects, it also acts as a sedative. Because it is low cost and easy to administer, it is commonly used in the developing countries though the effects are not consistent. Hypotension is a serious concern but can be easily tackled with inotropes. A case series of eight newborns was reported from Saudi Arabia (Daffa and Milaat 2002). The babies were given MgSO₄ 8 % dilution in a loading dose of 200 mg/kg, followed by a maintenance dose of 20–100 mg/kg/h with the aim to keep magnesium levels 3.5–5.5 mmol/L. Seven out of 8 patients showed marked improvement in partial pressure of oxygen at 6 h and maximum improvement at 24 h. A case series of 12 infants who were given magnesium in a similar protocol was reported from Brunei over a period of 2 years (Chandran et al. 2004). Dopamine was commenced at 5–10 μ g/kg/min before the loading dose of MgSO₄ was given. Mean blood pressure was maintained with short periods of dopamine alone or in combination with dobutamine. Oxygenation index (OI) and alveolar-arterial oxygen gradient (A-aDO₂) showed significant improvement within 24 h of treatment. In a recent randomised controlled trial, term infants with PPHN on high-frequency oscillatory ventilation (HFOV) were treated with either iNO or intravenous magnesium sulphate (Boo et al. 2010). Infants in the MgSO₄ group ($n=13$) were loaded with MgSO₄ 200 mg/kg infused over half an hour, followed by continuous infusion at 50–150 mg/kg/h to attain a serum magnesium level of 5.0–7.0 mmol/L.

Infants in the iNO group ($n=12$) were administered nitric oxide at an initial concentration of 20 ppm. There was no significant difference in the proportion of infants who responded primarily to either vasodilator (MgSO_4 23 %, iNO 33 %, $P=1.0$). After switching over to iNO following a failed MgSO_4 therapy, a significantly higher proportion (9 out of 10) of the nonrespondents in the MgSO_4 group recovered from PPHN and survived compared to the nonrespondents in the iNO group (1 out of 8) who switched over to intravenous MgSO_4 ($P<0.03$).

32.1.3.3.2 Milrinone

Milrinone, a phosphodiesterase (PDE) III inhibitor, is routinely used in paediatric cardiac intensive care units to improve inotropy and reduce afterload. Nine full-term neonates with severe PPHN (defined as oxygenation index [OI] >20 , failure of iNO therapy and echocardiographic confirmation of PPHN) received intravenous milrinone (McNamara et al. 2006). Intravenous milrinone was commenced at a median age of 21 h, and patients were treated for median of 70 h. Oxygenation index was significantly reduced after milrinone treatment, particularly in the immediate 24 h of treatment. Infants who received milrinone did not develop systemic hypotension; in fact, there was a non-significant trend toward improved blood pressure. Another study reported four cases with severe PPHN treated with a combination of iNO and milrinone (Bassler et al. 2006). All four cases were unresponsive to therapy including iNO, with a mean oxygenation index (OI) of 40 before milrinone. Substantial improvement in OI was followed by extubation and survival. However, of 4 patients, 2 developed serious intraventricular haemorrhages (IVHs), and 1 had a small IVH.

32.1.3.3.3 Adenosine

Adenosine infusion causes selective pulmonary vasodilation in fetal and neonatal lambs with pulmonary hypertension. Six consecutive cases of PPHN were treated with adenosine following failure of conventional therapy, excluding iNO

(Patole et al. 1998). A rise in arterial PO_2 >20 mmHg occurred in 5 of 6 cases within 30 min of commencing adenosine infusion. Individual maximal increases in PaO_2 ranged from 31 to 131 mmHg. Three neonates survived and 3 died. Among deaths, intensive support was withdrawn in a preterm neonate due to severe arthrogryposis/pulmonary hypoplasia. Of the remaining two, the improvement in oxygenation persisted until death occurred from causes unrelated to adenosine. Side effects related to adenosine (bradycardia, hypotension, prolonged bleeding time) did not occur. Due to its ease of availability, administration and extremely short half-life, adenosine may be an important therapeutic option in PPHN. In a randomised, placebo-controlled, masked trial comparing the efficacy of 25–50 $\mu\text{g/kg/min}$ intravenous infusion of adenosine to normal saline infusion over a 24 h period, 18 term infants with PPHN and arterial postductal PO_2 of 60–100 Torr on inspired O_2 concentration of 100 % and optimal hyperventilation (PaCO_2 <30 Torr) were enrolled (Konduri et al. 1996). Four of nine infants in the adenosine group and none of the placebo group had a significant improvement in oxygenation, defined as an increase in postductal PaO_2 of ≥ 20 Torr from pre-infusion baseline. Arterial blood pressure and heart rate did not change during the study in either group. The need for extracorporeal membrane oxygenation, incidence of bronchopulmonary dysplasia and mortality were not different in the two groups.

32.1.4 Corticosteroids

32.1.4.1 Systemic Steroids

32.1.4.1.1 RDS

Since antenatal steroids have been shown to be very useful in preventing and decreasing the severity of RDS, it was postulated that postnatal steroids started very early may be able to ameliorate the severity of RDS. Early (<12 h) postnatal dexamethasone therapy of varying duration from 3 days to 3 weeks has been shown to reduce pulmonary inflammation, oxygen requirements,

duration of ventilation and a trend to reduce CLD (Lin et al. 1999; Mukhopadhyay et al. 1998). However, steroids need time to induce the synthesis and secretion of surfactant, and the damage due to oxygen and ventilation usually takes place before steroids can have full-blown effects. In addition, there are serious concerns about adverse neurodevelopmental effects of early postnatal steroids as discussed in subsequent section. Hence, early postnatal steroids are not recommended for management of RDS.

32.1.4.1.2 CLD

Systemic steroids have been used early (<96 h of age) or moderately early (7–14 days) to prevent CLD. In addition, they have used late or delayed (>3 weeks of age) to treat CLD. Both early and moderately early approaches reduce the incidence of CLD at 28 days of life and 36 weeks' PMA (Halliday et al. 2003a, b). Moderately early steroids also reduce mortality at 28 days of age but early steroids do not (Halliday et al. 2003b). Although these benefits are achieved, there are serious side effects – hypertension, hyperglycaemia, gastrointestinal bleed, hypertrophic cardiomyopathy and infections (Committee on Fetus and Newborn 2002). Even more worrisome are increased incidence of cerebral palsy and neurodevelopmental delay reported in trials of early systemic steroids (Halliday et al. 2003a; Committee on Fetus and Newborn 2002). Limited information is available about the long-term follow-up of babies who received moderately early steroids. This has not shown any increase in adverse neurological outcomes (Halliday et al. 2003b). Delayed use of steroids causes lesser side effects but is also less effective showing no effects on mortality and minimal decrease in incidence of CLD at 36 weeks' PMA (Halliday et al. 2009a, b). Delayed use of steroids has also been linked with hypertension and neurological abnormalities. Because of the serious short- and long-term side effects, the American Academy of Pediatrics has recommended that steroids should not be routinely used in the prevention or treatment of CLD (Committee on Fetus and Newborn 2002).

32.1.4.1.3 Meconium Aspiration Syndrome

Since meconium induces a strong inflammatory response in the lungs, steroids could have potential benefit in MAS. Two small randomised controlled trials, however, have shown no improvement in survival, oxygen dependency at 28 days, duration of ventilation, air leaks or duration of hospitalisation (Wu et al. 1999; Ward and Sinn 2003). Rather, the duration of oxygen was more in those who received steroids.

32.1.4.1.4 Inhaled Steroids for CLD

It was thought that inhaled steroids by virtue of being directly delivered into the lungs in smaller doses may be more effective and have fewer systemic side effects. However, a Cochrane review of three trials conducted in ventilator-dependent preterm babies found no evidence that inhaled corticosteroids confer any advantages over systemic corticosteroids. There was no evidence of difference in effectiveness or side effect profiles for inhaled versus systemic steroids. Long-term follow-up data of babies who received inhaled steroids is also not available. The authors concluded that neither inhaled steroids nor systemic steroids can be recommended as standard treatment for ventilated preterm infants (Shah et al. 2007). The lack of effectiveness may be related to inadequacy of delivery systems. Hence, a better delivery system guaranteeing selective delivery of inhaled steroids to the alveoli might result in beneficial clinical effects without increasing side effects and needs to be tested.

32.1.5 Methylxanthines

This group of drugs which includes aminophylline, theophylline and caffeine has been used for years in the prevention and treatment of apnoea of prematurity and to prevent extubation failure. In a systematic review of 192 infants from five trials, there was a reduction in recurrent apnoea and the use of mechanical ventilation in the first 2–7 days of methylxanthine use (Skouroliaou et al. 2009). Caffeine is a better drug because of

its wide therapeutic index and once a day dosage. It is at least as effective as aminophylline and may be even more effective in the first week of life (Henderson-Smart and Steer 2001). In a large multi-country double-blind trial involving more than 2,000 infants of 500–1,250 g, which compared caffeine to placebo, the caffeine group received lesser supplemental oxygen and lesser days of ventilation (Schmidt et al. 2006). The rates of death, ultrasonographic signs of brain injury and necrotising enterocolitis did not differ significantly between the two groups. Even more reassuringly, the rates of death or neurodevelopmental disability at 18–21 months' corrected age were significantly lower in the caffeine group (Schmidt et al. 2007). This trial has led to widespread use of prophylactic caffeine in very low birth weight babies. In the developing world, caffeine is not easily available and is expensive, especially in view of its short shelf life. However, local pharmacies can often prepare caffeine solution from pharmacologic grade powder of caffeine. A Cochrane meta-analysis of six trials to study the prophylactic use of methylxanthine treatment for successful extubation observed a 27 % absolute reduction in the incidence of failed extubation, especially in babies less than 1,000 g and less than a week old (Henderson-Smart and Davis 2003).

32.1.5.1 Inhaled CO₂ for Apnoea

A small randomised controlled study of 42 preterm infants of gestational age 27–32 weeks suggested that inhaled low (0.8 %) CO₂ concentrations in preterm infants are at least as effective as theophylline in decreasing the duration and number of apnoeic episodes, have fewer side effects and cause no changes in cerebral blood flow velocity (Al-Saif et al. 2008).

32.1.6 Drugs for Patent Ductus Arteriosus (PDA) Closure

Presence of PDA increases the risk of CLD. Indomethacin has been used traditionally to close the ductus both intravenously and orally with equal success. The largest trial assessing outcomes

following prophylaxis with indomethacin, the international Trial of Indomethacin Prophylaxis in Preterms (TIPP), found a significant decrease in the frequency of PDA following indomethacin therapy (Schmidt et al. 2001). The incidence of IVH also decreases with indomethacin. There was, however, no decrease in the incidence of CLD. Indomethacin decreases blood flow to the brain, kidneys and gut and can increase the incidence of periventricular leukomalacia, gut injury and renal failure. Ibuprofen, another cyclooxygenase inhibitor, has been shown to be effective in PDA closure without reducing blood flow velocity to the brain, gut or kidneys. A Cochrane meta-analysis included 20 studies and found no statistically significant difference in PDA closure rates between indomethacin and ibuprofen (Ohlsson et al. 2010). The risk of developing necrotising enterocolitis (NEC) was reduced for ibuprofen (RR 0.68, 95 % CI 0.47, 0.99), and there was less evidence of transient renal insufficiency in infants who receive ibuprofen compared to indomethacin. Orogastric administration of ibuprofen was as effective as i.v. administration. Hence, ibuprofen currently appears to be the drug of choice.

32.1.7 Potential Drugs for Prevention and Treatment of BPD

32.1.7.1 Vitamin A

Vitamin A deficiency has been postulated to contribute to development of BPD because of the role of vitamin A in epithelial differentiation and maturation processes. Low serum concentrations of vitamin A in preterm infants have been associated with an increased risk for developing CLD. Tyson et al. reported increased vitamin A levels and reduced incidence of BPD after intramuscular supplementation of vitamin A for 28 days of life (Tyson et al. 1999). However, because of the necessity to give multiple i.m. injections, routine parenteral vitamin A supplementation is not in widespread use (Ambalavanan et al. 2004). Oral regimens have failed to achieve similar results. It remains to be seen whether a combined regimen of parenteral followed by oral vitamin A can be effective.

32.1.7.2 Vitamin E and Antioxidants

Vitamin E – an antioxidant and a scavenger of free radicals – has been extensively studied in preterm neonates. A systematic review of the vitamin E trials indicates that supplementation does not decrease the incidence of CLD (Brion et al. 2003). Superoxide dismutase, an antioxidant, has been tried in two small trials, but no benefit for prevention of CLD could be demonstrated (Rosenfeld et al. 1984; Wiswell et al. 2007).

32.1.7.3 Diuretics

Diuretics like furosemide, thiazides and spironolactone are commonly used in preterm babies with evolving or established CLD. They are used intravenously, orally and as aerosolised form. The purpose is to reduce alveolar and interstitial oedema. They, however, have numerous short- and long-term side effects on electrolyte balance, ototoxicity and nephrocalcinosis. Furosemide has been shown to cause short-term improvement in pulmonary functions (Brion et al. 2002). But there are no effects on ventilator settings, duration of ventilation, hospitalisation or mortality. Hence, diuretics should be used very sparingly and only for short duration.

Diuretics have also been tried for acute RDS and transient tachypnoea of newborn but have failed to show any benefits (Brion and Soll 2008).

32.1.7.4 Beta-Agonists

Hyperreactivity of airways is seen in babies with RDS and BPD, especially in those on mechanical ventilation. Salbutamol (albuterol) has been assessed in multiple short-term studies. Variable effects on pulmonary mechanics – improvement, no change or worsening – have been demonstrated in these studies. In a prevention trial in at-risk infants, no effect could be seen on mortality or occurrence of CLD (Denjean et al. 1998). None of the trials of bronchodilators in babies with ventilator dependency has assessed important clinical outcomes like death, CLD at 36 weeks or duration of oxygen (Ng et al. 2001). It is also not easy to deliver the bronchodilator

drugs in intubated neonates, and that may be an important factor causing wide variability in responses.

32.1.7.4.1 Other Bronchodilators

Anticholinergic agents like ipratropium bromide and mast cell stabiliser cromolyn Na have been used in case series or small trials of short-term use (Wiswell et al. 2007). Generally, the short-term effects are mixed and long-term effects unknown.

32.1.7.5 Erythromycin

Ureaplasma urealyticum has been commonly isolated from the tracheal secretions of preterm neonates on ventilator and has been implicated in the pathogenesis of CLD (Mabanta et al. 2003). Two small trials have assessed the efficacy of treatment with erythromycin in the prevention of CLD in intubated preterm infants at risk for or colonised with this organism (Jonsson et al. 1998; Lyon et al. 1998). No effect on death or on the development of CLD has been demonstrated in these studies.

32.1.8 Sedatives and Analgesics

32.1.8.1 Opioids

The presence of endotracheal tube and ventilation is painful to the preterm and term newborn. Multiple painful episodes have the potential to impair neurological outcomes and behaviour. However, the use of analgesics and sedatives, especially narcotics, has been problematic because of adverse effects, especially on the developing brain (Durrmeyer et al. 2010). Initial trials suggested that preemptive analgesia given by continuous low-dose morphine infusion may reduce the incidence of poor neurological outcomes in preterm neonates who require ventilatory support (Anand et al. 1999). However, large multicentre trials showed that placebo and morphine groups had similar rates of the composite outcome, neonatal death, severe IVH and PVL. Placebo-group neonates receiving open-label morphine had worse rates of the composite outcome than those not receiving open-label

morphine, while morphine-group neonates receiving open-label morphine were more likely to develop severe IVH (Anand et al. 2004). Hence, though it is realised that ventilated neonates feel pain and narcotic analgesics are effective in reducing pain, there are potential adverse effects on the developing brain which limit the routine use of these drugs (Bellù et al. 2005). These drugs are more commonly used in babies with PPHN or difficult ventilation and asynchrony. Of the two most commonly used opioids, fentanyl causes lesser hypotension but is more expensive and causes chest wall rigidity. Continuous low-dose infusions are better than bolus administrations of both the opioids.

32.1.8.2 Midazolam

Midazolam is not an analgesic and used as a sedative but has no advantages over morphine or placebo (Ng et al. 2003). It has more adverse outcomes in the form of hypotension, mortality, IVH and PVL, especially when used in bolus form. Hence, it is not recommended to be used in neonates.

32.1.8.3 Paralytic Agents

Paralytic agents have been used to improve ventilator-patient synchrony and have the potential to decrease air leaks and intracranial bleeds (Cools and Offringa 2005). However, they have serious side effects of hypotension, water retention and muscle atrophy ultimately leading to failure of weaning. In addition, the long-term pulmonary and neurological effects are uncertain and hence are not recommended for routine use.

32.1.8.4 Medications for Intubation

The Committee on Fetus and Newborn of the American Academy of Pediatrics recommends that except for emergent intubation during resuscitation either in the delivery room or after acute deterioration or critical illness at a later age, premedication should be used for all endotracheal intubations in newborns (Kumar et al. 2010). Medications with rapid onset and short duration of action are preferable, and there is a wide variety of drugs, often with limited experience, to choose from. In the developing world, this practice is yet to catch on.

32.1.9 Non-pharmacologic Interventions

Several other adjunctive strategies are often used in the management of neonates with respiratory failure. Two of them deserve mention here. The first is to use restricted fluids during the acute phase because extra fluids can 'open' the PDA, aggravate lung fluid and have been associated with CLD (Bell and Acarregui 2001). The second is the role of providing adequate nutrition to a sick and small baby. Very low birth weight babies rapidly catabolise, and an aggressive nutrition policy of providing adequate amino acids and lipids helps in lung growth and earlier weaning.

Essentials to Remember

- Single course of antenatal steroids, surfactant replacement therapy, inhaled nitric oxide and caffeine have been proven in large multicentre trials and meta-analysis to be beneficial therapies for prevention and treatment and carry minimal risks.
- Antenatal steroids are cheap and cost-effective but underutilised in both developing and developed countries. They improve many neonatal outcomes apart from respiratory distress.
- Early rescue SRT is cost-effective in RDS but is beyond the reach of a large proportion of populations in low-resource countries.
- iNO is well established as the mainstay of treatment of PPHN in term babies but needs further evaluation in preterms. iNO is currently, however, too expensive to be feasible in most of the developing world.
- Cheaper alternatives for PPHN like sildenafil, magnesium sulphate and adenosine hold a lot of promise but are yet to be subjected to rigorous large multi-centre trials.
- Caffeine has been shown to be safe and effective in very low birth weight babies in preventing apnoea and CLD.

32.2 In Paediatric Respiratory Failure

Andrew C. Argent

Educational Aims

- Consider the most common therapies that have been used as adjuncts to mechanical ventilation
- Discuss the evidence for and against the suggestion that these therapies may be useful in the setting of respiratory failure

A wide variety of therapies have been used as an adjunct to mechanical ventilation including surfactant, inhaled nitric oxide (iNO), inhaled vasodilators and helium-oxygen mixtures (heliox).

Many of these therapies are expensive (iNO may cost \$3,000 per patient day in the USA), and considerable caution should be exercised in any evaluation of the actual benefits of these therapies. A feature of all the adjunctive therapies is that while there are many reports of successful use of the specific therapy, there are relatively few randomised controlled studies. For most therapies large multicentre clinical trials with approximately 60 centres would be required to provide the evidence required to direct clinical use of these therapies (Santschi et al. 2010). At present there are only relatively small randomised trials available which are not adequately powered to exclude useful effects of the drugs, particularly in subcategories of patients. A further consideration in evaluating the effects of these adjunctive therapies is the design of randomised studies. As an example NO has been shown to improve oxygenation acutely in many studies of children with respiratory failure, but in most cases has not altered outcomes. However, many studies have not made clear the response to improved oxygenation following NO; it is possible that outcomes may be different if other therapies are altered as a result of improved oxygenation, while it may be unlikely that outcomes would be changed if all other therapies were unchanged following the use of NO.

In many intensive care units, adjunctive therapies are used (or at least tried) in many patients, despite limited evidence of benefit in the literature. Where resources are more limited, it may be difficult to make practical decisions regarding the appropriate use of these adjuncts. Most of the adjunctive therapies are manufactured or produced in more affluent countries where they are relatively inexpensive in comparison to staff salaries. In this setting, even small decreases in duration of PICU stay may make the therapy cost-effective (if there are no significant side effects). The converse may be true in poorer countries.

32.2.1 Surfactant

Surfactant is essential for stability of the normal lung and has a number of anti-inflammatory and anti-infective properties in addition to effects on surface tension (Lewis and Veldhuizen 2006).

Surfactant therapy has been well established in neonates (both preterm and term) with respiratory distress. A recent Cochrane review concluded that the use of animal-derived surfactant in infants with established respiratory distress syndrome was associated with decreased risk of pneumothorax, pulmonary interstitial emphysema, mortality and bronchopulmonary dysplasia or death (Seger and Soll 2009).

It is difficult to extrapolate results from either neonatal or adult studies to children. In neonatal respiratory distress syndrome, the underlying problem is surfactant deficiency. In acute respiratory distress syndrome and other causes of respiratory failure in children, there may be a wide variety of underlying pathologies (including infection, aspiration, systemic inflammatory responses, trauma) and there may be a range of lung pathology from ARDS/ALI to bronchiolitis. In adults severity of hypoxaemia in acute lung injury may not be an independent predictor of mortality, whereas it may be in children (Flori et al. 2005; Randolph 2009).

A meta-analysis of surfactant administration in adults with ARDS (6 trials accepted into the meta-analysis, 2 given by aerosolisation and 4

intratracheally) failed to show any survival benefit (Davidson et al. 2006). However, another meta-analysis suggested that there may be some subgroups of adults with ARDS, specifically those with pneumonia or aspiration syndromes who may benefit from surfactant therapy (Taut et al. 2008), using recombinant protein-C surfactant.

The role of surfactant therapy in children is more controversial although a recent review of surfactant therapy in children suggested that there were significant advantages and limited side effects (Duffett et al. 2007). Most studies of surfactant therapy in children (and adults) relate to patients with ARDS, ALI or hypoxaemic respiratory failure. There are a small number of studies on other sorts of respiratory disease.

There are several forms of surfactant available for therapeutic use. In neonates most studies have used animal-derived surfactants. These have been recently reviewed (Ramanathan 2009; Logan and Moya 2009). Although there is little difference between the animal-derived surfactants in terms of patient survival or development of chronic lung disease (neonatal studies), it appears that calfactant (bovine surfactant) and poractant (porcine surfactant) have an advantage over beractant (Survanta, a bovine extract) in terms of outcomes such as pneumothorax, ventilator weaning and need for supplemental oxygen. Recent data suggests that poractant may have significant advantages in terms of costs and mortality (Ramanathan 2009) in neonatal use. The use of synthetic surfactants has also recently been reviewed (Moya 2009), and while animal-derived surfactants have generally outperformed synthetic surfactants, a new-generation synthetic surfactant with higher levels of Sp-B-like activity may have potential for significant use.

There is no data in children comparing different forms of surfactant, and there is little information regarding the optimal methods of administration.

32.2.1.1 Acute Respiratory Failure, ALI and ARDS

A number of studies had suggested that children with acute respiratory failure could benefit from the administration of surfactant, and these are all shown in Table 32.1.

There are multiple potential methods for administration of surfactant which may have significant patient effects (Willson et al. 2005), but one group has tried bronchoscopic installation on the premise that this may help to reduce the amount of surfactant required (Nakamura et al. 2001).

A meta-analysis of six studies of acute respiratory failure (including ALI and bronchiolitis) in children (Duffett et al. 2007) showed decreased mortality and duration of mechanical ventilation, together with increased ventilator-free days.

A study of the cost-effectiveness of surfactant usage in the context of an American PICU was undertaken by Thomas et al. (2005). They analysed the data from a previous study (Willson et al. 2005) and showed that in that setting and with the assumption of hospital savings based on a decreased length of PICU stay, a hospital could expect to save \$11,084 per 10-kg patient with AHRF treated with surfactant. They suggested that a hospital could save \$269,684 for every life saved by using surfactant in every 10-kg child with acute hypoxic respiratory failure. In poorer countries these therapies are often much more expensive in comparison to staff salaries and other hospital costs, and the cost-effectiveness profile may be substantially different.

32.2.1.2 RSV and Bronchiolitis

A randomised controlled study of 20 infants with severe bronchiolitis (Luchetti et al. 1998) using porcine surfactant showed improvement in oxygenation and reduction of duration of ventilation in treated patients.

In a pilot randomised controlled study involving 19 infants with RSV-related respiratory failure, Tibby et al. (2000) reported that surfactant (Survanta, bovine surfactant) administration was associated with improvements in oxygenation and ventilation parameters over the following 60 h.

In a multicentre randomised controlled trial of the use of porcine surfactant in the management of RSV-related respiratory failure in children, Luchetti et al. demonstrated that surfactant administration was associated with improved respiratory mechanics and gas exchange and resulted in reduced periods of ventilation and PICU stay (Luchetti et al. 2002).

Table 32.1 Studies on the use of surfactant in children

Author	Year	Study	Outcome
Willson et al.	1999	42 children with hypoxaemic respiratory failure randomised to installation of bovine surfactant (Calfactant)	Reduction in duration of ventilation and PICU stay, but there was no difference in mortality
Lopez-Herce et al.	1999	Retrospective study of 20 children with acute respiratory failure	Porcine surfactant showed an improvement in oxygenation but not change in outcome
Hermon et al.	2002	Retrospective study of 19 children given surfactant (some porcine and others bovine surfactant)	Improvement in oxygenation
Herting et al.	2002	Surfactant (porcine surfactant – Curosurf) in 8 children with severe pneumonia or ARDS	Immediate improvements in oxygenation, but could not comment on outcomes
Moller et al.	2003	Randomised control study of children with ARDS (initially in single centre and then multicentre)	Significant improvement in oxygenation following administration of bovine surfactant. There was a higher survival in the surfactant group, but this was not statistically significant
Yapicoglu et al.	2003	Prospective study of 36 children with acute hypoxaemic respiratory failure (could not be done in a randomised fashion as not all patients could afford surfactant)	The mortality, length of stay and duration of ventilation were all reduced in the group receiving surfactant
Willson et al.	2005	A large multicentre study of bovine surfactant (Calfactant) in children with acute lung injury	Mortality was significantly reduced with surfactant with a number needed to treat of ± 6 . No difference in duration of PICU or hospital stay or duration of ventilation. Post hoc analysis showed that in immunocompromised children, surfactant use was associated with a significant reduction in mortality
Hermon et al.	2005	13 children on ECMO	Surfactant administration on ECMO was associated with an improvement in respiratory mechanics

In a meta-analysis of the three studies quoted above, Davison et al. (2004) concluded that the therapy looked promising but that the strongest effect on the data for duration of ventilation came from Luchetti et al. (1998) in which there was an unusually long duration of ventilation.

Thus, there is no data that surfactant therapy changes mortality in patients with severe bronchiolitis, but use may be associated with a decrease in duration of ventilation.

32.2.1.3 Other Lung Injury

A small randomised controlled study of ‘mediated saline’ (saline with porcine surfactant) in the management of unilateral lung contusion (Marraro et al. 2010) has recently been published, showing some benefits from surfactant.

A recent case report (Haas et al. 2006) reported on successful outcome following surfactant (Survanta) administration for a child with iatrogenic lung haemorrhage following surgery. Improvement with surfactant therapy has also been described in a 1-month-old infant following pulmonary haemorrhage (Neumayr et al. 2008).

Similarly, Marraro et al. (2007) randomised 20 children to receive either lavage (Curosurf and saline) or bronchial suction as therapy for severe aspiration. Children who received the therapeutic lavage had a more rapid improvement in oxygenation and a substantially shorter duration of ventilation (4.6 ± 1.07 vs. 11.8 ± 3.22 days, $P < 0.0001$).

As reviewed by Matthay and Taeusch (2007), these findings are encouraging, but all need to be submitted to much larger multicentre studies

(with standardisation of many aspects of management) before firm recommendations can be made.

There is both animal (Eijking et al. 1992) and human data (Slater et al. 1995; Creery et al. 1997) suggesting that surfactant therapy may be useful in patients with severe pneumonia related to *Pneumocystis jirovecii* infection.

Conclusion: There is strong evidence that there may be a role for surfactant therapy, particularly in patients with acute hypoxaemic respiratory failure. However, there is still debate about optimisation of the therapy, and it is possible with optimisation of ventilatory care for patients with severe lung disease that the role of surfactant may change.

32.2.2 Pulmonary Vasodilators

32.2.2.1 Inhaled Nitric Oxide

There have been many studies of the use of iNO in neonates in respiratory failure. Many of the studies were summarised by Finer and Barrington (2006b) in a Cochrane review. They concluded that there was no evidence that use of NO decreases mortality, although it decreases the need for ECMO (number needed to treat is 5.3).

As there appear to be few long-term sequelae, it may be reasonable to use it in hypoxic neonates.

iNO has been clearly shown to improve oxygenation in ARDS in children even at low doses (Tang et al. 1998). However, in 2007 the only FDA-approved indication for inhaled NO was term and near-term (34 weeks) neonatal hypoxaemic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension (Ryan and Tobias 2007).

Reported studies of NO use in children are shown in Table 32.2.

If iNO is used, there is invariably a deterioration in oxygenation with weaning, and this must be addressed (either sildenafil or acceptance of lower sats) (Moledina et al. 2010; Barach 1934).

Children who are being ventilated following cardiac surgery may benefit from iNO. Cai et al. have demonstrated benefits from milrinone and NO following the Fontan procedure (Cai et al. 2008).

An additional consideration in the analysis of the use of NO was highlighted by Kinsella and Abman (1998). In their study of HFOV and iNO (Kinsella et al. 1997), 23 % of infants treated with HFOV had a successful response (defined as PaO₂ >60 mmHg) compared to 28 % of infants treated with iNO. After crossover, 21 % of the 75

Table 32.2 Studies of NO use in children

Author	Year	Study	Comment
Day et al.	1997	Randomised control study of iNO in 24 patients with acute lung injury (admission criteria: acute bilateral CXR infiltrates, PEEP >6 cm H ₂ O, FiO ₂ >0.5 for >12 h) at an initial dose of 10 ppm	iNO was associated with immediate improvements in oxygenation. There was no evidence of a difference in outcome related to its use
Dobyns et al.	1999	A large multicentre study of children with acute hypoxaemic respiratory failure	Although iNO was associated with improvements in oxygenation, there was no evidence for an overall improvement in outcome. Subgroups (immunocompromised and those with an oxygenation index on admission of >25) might benefit from more prolonged use
Fioretto et al.	2004	Randomised controlled study of 39 children aged 1 month to 12 years with ARDS	Early administration of iNO was associated with a rapid and sustained improvement in oxygenation. There were no differences in mortality or duration of ventilation between the groups
Ryan and Tobias	2007	Review of 5 years of iNO use in a PICU in the USA	In 19 patients who received iNO for hypoxaemic respiratory failure, all 15 who improved oxygenation on iNO survived, while none of the 4 who did not respond survived

HFOV ‘failures’ responded to iNO, whereas 14 % of 77 iNO ‘failures’ responded to HFOV (not significant). When patients who failed to respond to either therapy on its own ($n=125$) were treated with a combination of NO and HFOV, 32 % responded to the combination. As concluded by the authors, establishment of adequate lung volumes may be a prerequisite for effective NO use.

Recently, use of iNO in a patient with severe hypoxia related to fat embolism was reported (Amigoni et al. 2010). Administration of iNO while on HFOV was associated with an immediate improvement in oxygenation. The child went on to recover from the injury.

iNO is expensive, with estimated daily cost in the USA being approximately \$3,000 (Ryan and Tobias 2007). However, there is some data that sildenafil may have equivalent activity to iNO at considerably lower cost (Huddleston et al. 2009; Vida et al. 2007).

Conclusion: iNO has been clearly demonstrated to improve oxygenation in many settings of respiratory failure in children. However, the agent is expensive, and there is very limited evidence that use in paediatric respiratory failure is associated with improvements in patient outcome. One of the problems is that many patients with respiratory failure die of reasons unrelated to respiratory failure, making it difficult to evaluate the role of iNO in therapy. In addition none of the studies of iNO in children have been adequately powered to exclude potential benefits from iNO. We know that it is expensive and that in groups of patients there may not be obvious benefit. However, we have not excluded the possibility that there are cohorts of patients in which it may be effective.

32.2.2.2 Inhaled Vasodilators

Inhaled aerosolised prostacyclin has been shown to improve oxygenation in children with ALI (Dahlem et al. 2004). In a group of 14 children with ALI, a range of doses of aerosolised prostacyclin were compared with saline. In 8 of 14 children, there was a >20 % improvement in oxygenation, and the number needed to treat was 1.8 (95 % confidence interval, 1.2–3.2) (Dahlem et al. 2004).

32.2.3 Heliox

In 1934, Barach (1934) first suggested that helium-oxygen (heliox) mixtures could be used for patients with airway obstruction, and Gupta and Cheifetz have recently extensively reviewed the uses of heliox in the PICU setting (Gupta and Cheifetz 2005). Helium is an inert gas with a density one-seventh of that of air. The low density means that gas flow in obstructed airways is likely to be more laminar, and even when flow remains turbulent, there will be higher flow with helium mixtures than with air or nitrogen mixtures (Gupta and Cheifetz 2005). In addition CO₂ diffuses through helium four to five times faster than through air (Gupta and Cheifetz 2005). Thus, it has been used in many settings for the management of patients with airway obstruction (ranging from small to large airways) (Gupta and Cheifetz 2005). The differences in gas characteristics between oxygen-air mixtures and oxygen-helium mixtures depend on the amount

Theoretical basis for the use of Heliox

Laminar flow rate (Q) through a tube is determined by the Hagen-Poiseuille equation: $Q = \Delta P \pi r^4 / 8 \eta l$ where ΔP is the pressure drop, r is the radius, η is the gas viscosity and l is the length. Because the viscosity of helium, nitrogen and air are similar, heliox has little effect on laminar flow. As airway resistance increases, there is a critical level at which the flow pattern changes from laminar to turbulent. This transitional zone is defined by Reynolds number (Re): $Re = 2Vr\rho/\eta$ where ρ is the gas density and V is gas velocity. Thus, helium with its lower density will decrease Reynolds number in airways where resistance is high and may change turbulent flow into a more laminar pattern. Furthermore, where flow is turbulent, flow rate is dependent on gas density according to the Bernoulli equation: $Q = (2\Delta P/\rho)^{1/2}$. Therefore, with a lower gas density, helium may provide a higher flow rate even if flow remains turbulent (Tibby et al. 2000).

of helium present, and at high oxygen concentrations, there will be minimal differences. Thus, the addition of helium to inhaled gases is only likely to have clinical benefits if the inspired oxygen concentration is <80 %.

Unfortunately, the same characteristics that may improve respiratory mechanics will also profoundly affect the functioning of pneumotachometers with implications for ventilator and respiratory monitoring equipment (Brown and Willms 2005; Berkenbosch et al. 2003). If heliox mixtures are to be used in the clinical setting, great care must be taken to ensure that gas characteristics are taken into account on all respiratory equipment. Great care must be taken to ensure that there is no chance of giving hypoxic gas mixtures (if using 100 % helium gas supplies) or of cooling patients (helium has four to six times the thermal conductivity of nitrogen). Unfortunately, there are very few large randomised studies of heliox use in children, with numerous case reports and small studies in the literature (Myers 2006).

32.2.3.1 Asthma

On theoretical grounds heliox would be expected to be useful in the management of acute severe asthma. Heliox may be used both as a driver for bronchodilator nebulisation or as the primary gas for inhalation.

There are a number of adult studies suggesting that heliox may be useful, but there are very few paediatric studies available.

Carter et al. (Carter et al. 1996; Carter and Moffitt 1997) studied a group of non-ventilated children with severe asthma (using 70 % helium, 30 % oxygen) and concluded that although there were statistically significant improvements in lung function, 'the short-term inhalation of heliox did not benefit this group of children'. Kudukis et al. (1997) studied 18 patients with acute severe asthma (on therapy with steroids and inhaled beta-agonists). They found that use of heliox (80 % helium, 20 % oxygen) improved symptom scores and spared 3 patients a planned intubation.

Bigham et al. (2010) studied the effects of heliox-driven β_2 -agonists in children with severe

asthma in a randomised control trial. Importantly, they screened 1,277 children with status asthmaticus, and 690 were ineligible as they had responded to usual treatment for severe asthma. A further 268 patients failed enrolment, and 76 of those were not enrolled as their severity score had improved further. Thus, a small proportion of children with status asthmaticus had not responded adequately to usually emergency room therapy (with β_2 -agonists, steroids, magnesium sulphate, etc.). In the 42 children entered into the randomised study, they were not able to show any differences in rates of improvement or duration of hospital stay between the groups.

32.2.3.2 RSV and Bronchiolitis

At least one study has suggested that heliox did not improve gas exchange in children with bronchiolitis (Gross et al. 2000).

In a small study of 13 infants with severe RSV-related bronchiolitis, it was shown that heliox reduced the respiratory system resistance, but did not result in improved ventilation or carbon dioxide removal (Kneyber et al. 2009).

In a crossover study of 12 infants in PICU with severe bronchiolitis, administration of nasal CPAP with heliox resulted in significant decreases in clinical score and transcutaneous $p\text{CO}_2$ without any adverse effects relative to patients receiving nasal CPAP with an air-oxygen mixture (Martinon-Torres et al. 2008).

In a Cochrane review, Liet et al. (2010) reviewed 4 studies (involving 84 infants with RSV-related bronchiolitis) of the use of heliox administration in severely ill infants in paediatric intensive care. While use of heliox was associated with a significant decrease in respiratory distress scores, there was no difference in the incidence of subsequent endotracheal intubation and mechanical ventilation. There were no adverse effects reported.

32.2.3.3 Croup

Heliox has been used in many patients with upper airway obstruction such as croup. However, a recent review (Vorwerk and Coats 2010) concluded that although there are many anecdotal

reports of positive responses to therapy with heliox in croup, there is inadequate data to recommend that heliox be used routinely in this situation.

32.2.3.4 Chronic Lung Disease of Prematurity

When 10 preterm infants who had been ventilated for >8 days (mean 22 days) were changed to a heliox mixture, there was a reduction in the pressures generated to provide set tidal volumes, a reduction in work of breathing and an increase in minute ventilation. Eight of these infants met criteria for extubation onto CPAP with heliox (Migliori et al. 2009).

32.2.3.5 Specific Cases

Despite the equivocal results of studies quoted above, there are consistently case reports of individual patients who have responded to therapy with heliox, including a neonate with congenital airway obstruction (Tsai et al. 2009), a child with inhaled foreign body (Brown et al. 2002) and a preterm infant with severe localised pulmonary interstitial emphysema (Phatak et al. 2008).

In a single case report, use of heliox in an infant on high-frequency jet oscillation resulted in a dramatic improvement in CO₂ elimination and allowed weaning of ventilation (Gupta et al. 2004).

In a study of five patients with hypercarbic respiratory acidosis on high-frequency ventilation, introduction of heliox mixtures into the system resulted in significant improvements in CO₂ levels (Winters et al. 2000).

Conclusions: Although heliox has been reported to improve individual patients, although it has theoretical benefits and tantalising experimental evidence for benefits (Nawab et al. 2005) and although there may well be patients who derive benefit from helium-oxygen mixtures, there is little evidence to support widespread clinical use.

The gas is expensive and there are potential dangers in using helium in ventilatory systems that are not appropriately modified. Thus, it may be reasonable to use helium gas mixtures with great caution in some specific situations; it is unlikely to afford significant benefit to many patients.

32.2.4 Conclusions

Agents such as surfactant (in different forms), nitric oxide and heliox have been used in many situations as adjunctive therapy for ventilation or respiratory failure. Although there is anecdotal and in some cases randomised controlled data to justify their use in patients with respiratory failure, there is much that requires further investigation before ideal recommendations can be made for further use. It is likely that optimisation of current ventilatory practice will provide more benefits to more patients than use of these expensive agents.

Learning Points

- Although there are many reports on the use of adjuncts to ventilation, there is limited data indicating that they really make a difference to patient outcome. An exception to this is the use of surfactant in patients with severe lung disease.
- Despite lack of evidence of use, there is also inadequate evidence to exclude the possibility that the adjunctive agents described above may significantly improve patient outcomes.
- In countries with limited resources, the relative benefits to be obtained from use of these agents are probably strongly outweighed by the costs. This may not be true in more affluent countries.

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Part XI

Complications of Mechanical Ventilation

33.1 Introduction

Mechanical ventilation saves the lives of those who would otherwise rapidly die from respiratory failure. Very early in its use it became clear, however, that mechanical ventilation could lead to adverse effects (*i.e.*, ventilator-associated lung injury, VALI).

In 1939, Macklin reported that excessive alveolar distention led to the rupture of the junction between the alveolar wall and the vascular sheath, resulting in the tracking of air into the mediastinum, subcutaneous tissue, and/or pleural cavity (Macklin 1939). In the 1960s, it was shown that high tidal volumes (V_T) and the absence of positive end-expiratory pressure (PEEP) adversely affect lung compliance and surfactant function (Faridy et al. 1966; Greenfield et al. 1964). During the polio epidemics in the 1950s, it was occasionally

observed that patients ventilated with such injurious parameters developed lung lesions similar to those seen in the infant respiratory distress syndrome, *i.e.*, dense cellular infiltrates, edema, and hyaline membranes; this presentation was termed “respirator lung.” Later, the acute respiratory distress syndrome (ARDS, at that time termed adult respiratory distress syndrome) was described with similar morphology (Ashbaugh et al. 1967), but the role of mechanical ventilation in contributing to the injury was not appreciated.

Most of the patients in the initial case reports were suffering from underlying lung disease, and it remained unclear to what degree the ventilator contributed to the pathological picture observed at necropsy. This difficulty persists today in the clinical setting. The term ventilator-associated lung injury (VALI) accounts for this difficulty and describes the assumed

additional lung injury inflicted by a mechanical ventilator in patients with underlying lung disease (as opposed to the expression ventilator-induced lung injury [VILI], used to describe the lung injury induced exclusively by the ventilator, usually in animal models). However, the relative contributions of the underlying disease (*e.g.*, ventilator-associated pneumonia) and the injury caused by the ventilator are never fully known.

ARDS has an annual incidence of roughly 75 per 100,000 (Rubenfeld et al. 2005) with an overall mortality in adults of 60 % (Ferguson et al. 2005), and in children, mortality may be in the range of 22 % (Flori et al. 2005). Because of the impossibility of dissecting out the contribution of the mechanical ventilator to the lung injury in the clinical setting, most evidence in the field comes from laboratory-based studies (*i.e.*, VILI), using short-term animal models.

Does VILI or VALI present differently in children than in adults? There is some evidence that lungs of children and infants have a lower susceptibility to high ventilator settings compared to adults (Copland et al. 2004; Kornecki et al. 2005). Nevertheless, the overall risk of adverse effects from mechanical ventilation is high in younger (specially preterm) infants because of the small lung size (Jobe and Ikegami 1998), highly compliant chest wall, and immaturity of surfactant and defense mechanisms, in addition to associated comorbidities (see Sect. 33.3.3).

This chapter summarizes the current knowledge on the mechanisms of VILI, the clinical presentation, discusses predisposing factors, and outlines conventional and novel therapeutics useful in the prevention and management of lung injury during mechanical ventilation.

33.2 Lung Injury in the NICU

Pierre-Henri Jarreau

Educational Aims

- Understanding the main physiological factors that are implicated in neonatal VLI
- Taking these into account when modifying ventilator settings
- Knowing the treatment concepts and ventilator strategies that might help to prevent neonatal VLI

The development and large-scale implementation of mechanical ventilation in the field of neonatology has dramatically improved the survival rate of many high-risk neonates, especially preterm infants. As with all treatment modalities, mechanical ventilation has been accompanied by certain complications. The consequences in the form of long-term sequelae essentially concern very preterm infants, and this chapter will therefore focus on bronchopulmonary dysplasia (BPD) or chronic lung disease of prematurity. This disease was unknown before the introduction of mechanical ventilation for premature newborns, and mechanical ventilation was initially considered to be the main cause of BPD. This was probably true in the first descriptions, but host factors, particularly severe immaturity, now appear to be major factors, which explains the relative stability of the incidence of BPD despite advances in respiratory care of these babies.

33.2.1 Predisposing Risk Factors

The lung of preterm infants is subjected to the same mechanisms of injury as the lung of older

children and adults, but these mechanisms are exacerbated due to the particular state of development of the lung. Briefly, the formation of alveoli begins around 35 weeks of pregnancy, but extends into postnatal life. Extremely preterm infants have to breathe and often need to be ventilated while their lungs are still at the canalicular or early saccular stage of development. This abnormal situation leads to alveolar developmental arrest due to interferences with developmental mechanisms at multiple levels. Alveolarization involves the regulated expression of several genes and biological factors in various lung cell types (Bourbon et al. 2005) that act synergistically at a precise time of lung development. Many studies, based on animal models or human disease, indicate abnormal expression of gene products essential for the control of distal pulmonary development, induced by oxygen, mechanical ventilation, or airway inflammation as these injuries occur in a particular period of life.

The specific characteristics of respiratory mechanics of preterm infants, discussed in another chapter, may increase the risk of lung injury. In particular, surface tension is increased during the first hours of life (Greenspan et al. 2004) and is very high in the case of surfactant deficiency, responsible for respiratory distress syndrome (RDS), drastically reducing lung compliance and preventing the infant from maintaining functional residual capacity. In addition, infants with RDS have a lower total lung capacity (TLC), and thus, the lung volume between FRC and TLC may be low, increasing the risk of volutrauma (Attar and Donn 2002). This surfactant deficiency makes the preterm lung more susceptible to overdistention and atelectrauma leading to subsequent injury (Jobe 2006). Additionally, distribution of exogenous surfactant may be heterogeneous, which may be responsible for

uneven ventilation and atelectasis. Surfactant deficiency also results in pulmonary edema (Jobe 2006).

The relative deficiency of preterm infants in antioxidant systems makes them very susceptible to reactive oxygen species (ROS)-induced injury, even at low partial pressure of oxygen. In fact, several antioxidant enzymes are upregulated late during fetal development to help newborns adapt to an environment with a relatively high level of oxygen. Thus, premature infants lack sufficient levels of antioxidant enzymes because this upregulation of antioxidant enzymes occurs during the last 3 months of pregnancy (Asikainen and White 2004; O'Donovan and Fernandes 2004).

Other factors like antenatal inflammation, persistent ductus arteriosus, lung fluid retention, and malnutrition may participate or worsen the consequences of neonatal lung injury.

33.2.2 Mechanisms of Lung Injury in the NICU

The main purpose of the lungs is to ensure gas exchange, which requires inward flow of fresh gases obtained by a pressure gradient between the mouth and the lung. During spontaneous ventilation, this gradient is ensured by a negative pressure mainly induced by contraction of the diaphragm. Expiration is passive by a recoil force of distended elastic elements of the respiratory system. During mechanical ventilation, the pressure gradient (except for negative pressure ventilation) is created by the ventilator, which imposes a pressure and a volume on the lung which are primarily responsible for lung injury by inducing barotrauma and volutrauma (Attar and Donn 2002). In addition to these mechanical factors, oxygen appears to be a major factor inducing arrested alveolarization. Airway inflammation

associated with or induced by these factors also constitutes a major feature.

The few published autopsy studies have identified several common features in all infants with severe “old” or “new” BPD. Since the systematic use of surfactant and better control of all factors of lung injury, airway lesions and extensive fibrotic lesions are no longer observed or remain only minimal. On the other hand, signs of arrested alveolar development, clearly present on the first histological descriptions, now represent the almost exclusive lesion of BPD (Jobe 1999).

33.2.2.1 Mechanical Ventilation: Barotrauma, Volutrauma, and Atelectrauma

Experimental data show that both high peak pressures (barotrauma) and high tidal volumes (volutrauma) can cause lung injury. In the early 1990s, Dreyfuss et al. demonstrated that markers of lung injury are mainly linked to high tidal volume rather than to high pressures (Dreyfuss and Saumon 1998). To these two factors must be added atelectrauma, linked to alveolar instability, which is the result of repeated collapse and reopening of alveoli and respiratory bronchioles during the respiratory cycle (Schmolzer et al. 2008). These repeated reinflations from atelectasis impose a high shear stress on the alveoli. They also alter surfactant structure and function (Miller and Carlo 2008).

These mechanical factors may affect normal development by disturbing the expression of genes involved in normal development. Mechanical stretch of fetal lung epithelial cells activates various signaling pathways, resulting in transient or progressive increases in gene expression (Copland and Post 2007). Experimental data in preterm animals (lambs and baboons) or in species in which alveolarization is essentially postnatal (rodents) confirm these effects. Elastogenesis was disrupted, and elastic fibers displayed abnormal features in a lamb model of BPD (Bland et al. 2007b) or in ventilated mice (Bland et al. 2007a, 2008). Elastin is crucial for septal development (Bourbon et al. 2005), and

elastic tissue is altered in BPD (Thibeault et al. 2000). Other extracellular matrix components such as matrix metalloproteinases are involved in lung development and are altered in BPD, at least in human neonates (Danan et al. 2002b). In ventilated preterm baboons, pulmonary microvasculature is abnormal with a decrease of certain angiogenic factors such as VEGF (Maniscalco et al. 2002). This disrupted vasculature has been confirmed in human preterm infants with BPD (Thibeault et al. 2004). Other growth factors involved in lung development can be involved in neonatal lung injury. Fibroblast growth factor-7 (FGF7 or keratinocyte growth factor) has been shown to be higher in the first 5 days of life in human preterm infants who survived without BPD (Danan et al. 2002a). This opens the way to adjuvant therapies which may be proposed in order to prevent VILI. The preventive effect of FGF7 on VILI has been demonstrated in an adult rodent model (Welsh et al. 2000), but at the moment, this protective effect has not been demonstrated in neonatal experimental models in which alveolarization is not restored (Franco-Montoya et al. 2009).

Atelectrauma per se is deleterious, as demonstrated by Muscedere who showed, in a model of ventilated isolated lavaged lungs, that ventilation with PEEP below the inflection point increased lung injury (Muscedere et al. 1994). Moreover, lung collapse implies the use of higher peak pressures and larger tidal volumes in order to reexpand the lung, leading to a synergistic increase of lung injury. Lung recruitment is therefore a crucial element to minimize lung injury.

33.2.2.2 Oxygen Therapy

It has been known for a long time that BPD is closely linked to oxygen therapy. The mechanisms of oxygen injury have been discussed in detail elsewhere (Maltepe and Saugstad 2009). Hyperoxia is a widely used model of arrested alveolar development in rodents (Randell et al. 1989) and can be used to study the disruption of the normal factors of alveolar development. For

example, rat pups exposed to hyperoxia exhibit disruption of elastic fibers (Bruce et al. 1989) and elastin synthesis and assembly (Bland et al. 2007b) and a decrease in alveolar cell expression of vascular endothelial growth factor (Lopez et al. 2006; Maniscalco et al. 1997) or several other growth factors (Bland et al. 2007a; Wagenaar et al. 2004). The effect of oxygen may increase events that occurred antenatally, namely, prenatal inflammation (Choi et al. 2009) and induce inflammation as described below.

33.2.2.3 Inflammation

Finally, and closely linked to the previous factors, inflammation is one of the prominent mechanisms of lung injury. It results from treatments such as oxygen, leading to the generation of reactive oxygen species. It also results from volutrauma and atelectrauma that, along with reactive oxygen species and local inflammation or bacterial colonization, induce an inflammatory response that plays a major role in the pathogenesis of BPD. This inflammation may be self-perpetuating, accounting for residual damage leading to chronic lung injury.

Increased concentrations of proinflammatory cytokines have been detected in the amniotic fluid and in tracheal aspirate within hours after birth in newborns who subsequently developed BPD (Speer 2009). Thus, “fetal inflammatory response syndrome” is usually considered to be a causative factor of BPD, although this factor is more controversial in the clinical setting (Kent and Dahlstrom 2004; Richardson et al. 2006). BPD is associated with an inflammatory response of the airways characterized by the presence of neutrophils and activated macrophages, high concentrations of proinflammatory cytokines and chemokines (IL-8, TNF- α , IL-1, IL-6), and increased expression of ICAM adhesion molecules and L-selectin that trigger the recruitment of circulating neutrophils (Speer 2006, 2009). Large numbers of activated neutrophils invade the airspaces within hours after birth and persist during the first week of life in the airways of infants with BPD (Merritt et al. 1983). Further

lines of evidence suggest that neutrophils of preterm infants who develop BPD are less prone to undergo apoptosis (Hanna et al. 2005; Oei et al. 2003). Blood cytokines have been shown to be elevated in infants evolving toward BPD or death (Ambalavanan et al. 2009). Experimental induction of a pulmonary inflammatory response in neonatal animals is associated with disorders of alveolar development (Franco et al. 2002). Neutrophil influx, which is triggered by mechanical ventilation in preterm animals (Carlton et al. 1997), plays a crucial role. Rat pups treated with antibodies to the neutrophil chemokine cytokine-induced neutrophil chemoattractant-1 (CINC-1) during 95 % O₂ exposure present reduced adverse effects of hyperoxia-induced inflammation on lung development (Auten et al. 2001b). Many iatrogenic factors such as mechanical ventilation (Ricard and Dreyfuss 2001; Tremblay et al. 2002) or oxygen therapy are able to induce an inflammatory response as well as bacterial infections (Akram Khan et al. 2006; Ehrenkranz et al. 2005; Maxwell et al. 2009).

Inflammation, presence of reactive oxygen species, and disturbance of normal biological mechanisms of alveolar development can account for what is called “biotrauma.”

33.2.2.4 Immediate Consequences of Lung Injury

The main consequences of ventilator-induced lung injury (VILI) can be summarized as (Auten et al. 2001a; Miller and Carlo 2008):

- Alveolar capillary leak: high tidal volumes result in the disruption of alveolar and airway epithelium, basement membranes, and pulmonary capillary endothelium, a process which leads to fluid and protein leaks and exacerbates respiratory failure.
- Surfactant inactivation by proteins and serum components which add to surfactant deficiency if present, thereby increasing surface tension and worsening capillary leaks.
- Inflammation: mechanical ventilation increases accumulation of inflammatory cells and mediators in the lung. In experimental studies,

the greatest increase in proinflammatory cytokines is linked with high inflation pressures and high tidal volume.

- Air leaks: the mechanisms of which are discussed in another chapter, particularly, pulmonary interstitial emphysema which is an important factor of progression to BPD.
- Distal organ effects linked to the systemic diffusion of inflammatory cells and soluble mediators.

33.2.3 Treatment Options for Lung Protection

Mechanical ventilation settings that can increase or decrease lung injury are therefore:

- Oxygen therapy: oxygen must be considered as a potentially very harmful drug for the lung that is certainly involved in biotrauma, especially in preterm infants.
- Continuous positive airway pressure (CPAP): introduced by Gregory in 1971 (Gregory et al. 1971), the use of CPAP (also termed PEEP) rapidly became a standard of ventilatory care. It is an essential means to limit atelectrauma, as it maintains FRC and consequently alveolar inflation during expiration. It has been proposed to combine PEEP with recruitment maneuver in order to reopen collapsed alveoli, also known as open lung ventilation (van Kaam and Rimensberger 2007).
- Peak inspiratory pressure: it determines the tidal volume and is thus necessary in mechanical ventilation, but it may be responsible for barotrauma, volutrauma, and lung over-expansion.
- Mechanical ventilation rate, inspiratory time, and inspiratory/expiratory ratio.
- The resultant of these combined settings, mean airway pressure which may also be involved in neonatal lung injury (Greenspan et al. 2004).

Prevention of lung injury can therefore be summarized as (van Kaam and Rimensberger 2007) prevention of volutrauma by limiting tidal volumes, as performed in adults, and application of PEEP to maintain FRC and reopen collapsed

alveoli by recruitment maneuvers. The various ventilation modes that can achieve these combined goals and their results on the main consequence of neonatal lung injury, bronchopulmonary dysplasia, are discussed below. Prevention of air leaks is discussed in another chapter.

33.2.4 Practical Measures to Reduce the Likelihood of VILI in Neonatal Patients, e.g., to Prevent BPD

33.2.4.1 Predisposing Factors

Bronchopulmonary dysplasia (BPD) is the main consequence of VILI in neonatal period. This disease first described by Northway at the end of the 1960s as the major form of respiratory sequelae observed in preterm infants (Northway et al. 1967). The main clinical characteristic of this disease is the need for prolonged supplemental oxygen in preterm infants. This oxygen dependence constitutes the common denominator of the various definitions of BPD proposed since its first description. Two evaluation periods have been proposed: 28 days after birth and at the corrected age of 36 weeks of gestation. Evaluation at 36 weeks of gestation was very rapidly found to be more closely correlated with medium-term and long-term respiratory outcome than the evaluation at 28 days (Ehrenkranz et al. 2005; Shennan et al. 1988).

BPD is essentially a disease of very preterm infants. In Europe, the mean BPD rate at 36 weeks of gestation is 15.8 % in preterm infants born before 32 weeks, with variations of 10.5–21.8 % between countries (Zeitlin et al. 2008). Data from the National Institute of Child Health and Human Development Neonatal Research Network show a mean BPD rate at 36 weeks of 22 % in preterm infants with a birth weight less than 1,500 g (Fanaroff et al. 2007). The BPD rate is closely correlated with the degree of prematurity. At a gestational age of 36 weeks, 46 % of preterm infants with a birth weight less than 750 g have BPD compared to 33 % of infants with a birth weight between 750 and 1,000 g and

10 % of those with a birth weight between 1,000 and 1,500 g (Fanaroff et al. 2007).

Several parameters related to the infant itself and its environment have been identified as independent risk factors for subsequent development of BPD. Independently of inflammatory and infectious factors, the duration of postnatal exposure to oxygen and the duration of mechanical ventilation are very significantly correlated with the risk of subsequent BPD (Akram Khan et al. 2006). Hemodynamic factors also play a predisposing role, such as persistence of a patent ductus arteriosus (Akram Khan et al. 2006) or the need for repeated plasma expansion (Korhonen et al. 1999; Oh et al. 2005).

However, the major risk factor is host immaturity, as the incidence of BPD increases very significantly with the degree of prematurity (Akram Khan et al. 2006; Ehrenkranz et al. 2005). Moreover, small gestational age infants have an increased risk of BPD (Ehrenkranz et al. 2005; Korhonen et al. 1999). Genetic susceptibility factors have also been proposed (Bhandari et al. 2006; Lavoie et al. 2008).

The first descriptions of BPD generally referred to infants with respiratory distress syndrome (RDS) mechanically ventilated with supplemental oxygen, and the prevention of BPD was initially focused on these aspects: prevention and treatment of RDS, improvement of mechanical ventilation, and control of oxygen therapy, which remain the objectives of respiratory support in NICU.

33.2.4.2 Prevention of Mechanical Ventilation-Induced Lung Injury

33.2.4.2.1 Antenatal Steroid Therapy

Steroids constitute an essential treatment during threatened preterm delivery, and the efficacy of this treatment for the prevention of RDS has been very largely demonstrated. As they limit the need for mechanical ventilation, it could have been expected an effect on lung injury. In fact, data concerning the efficacy of steroids on BPD are contradictory (Van Marter et al. 1990, 2001), but, globally, meta-analyses do not clearly demonstrate any beneficial prophylactic effect on BPD (Roberts and Dalziel 2006) regardless of the type of steroid used (Brownfoot et al. 2013).

33.2.4.2.2 Respiratory Support in the Delivery Room

Improved management in the delivery room is probably one of the main factors of prevention of the development of BPD, as lung lesions can be induced in the first minutes of life (Jobe et al. 2008). The harmful effect of large tidal volumes immediately after birth has been extensively studied experimentally (Hillman et al. 2007; Ikegami et al. 2000). The choice of prolonged inspiration rather than large tidal volume ventilation has been proposed to establish FRC. A randomized trial compared the use of prolonged high pressure inspiration followed by early initiation of nasal CPAP vs. conventional management consisting of mask ventilation and initiation of nasal CPAP in the intensive care unit. The first strategy allowed a reduction of the BPD rate (te Pas and Walther 2007), confirming the importance of limiting the tidal volume during the first minutes of life and the value of prolonged insufflation to establish FRC. Current ILCOR guidelines recommend limiting insufflation pressures to less than 20 cm H₂O (ILCOR 2006).

33.2.4.2.3 Exogenous Surfactants

Exogenous surfactants, by limiting the aggressiveness and duration of mechanical ventilation, raised great hopes for the prevention of BPD. The administration of exogenous surfactants in infants with RDS is effective to prevent the combined risk of death and BPD, but generally not the risk of BPD alone (Soll 2000, 2010). The efficacy of surfactants is more marked when they are administered early, within the first 2 h of life (Yost and Soll 2000), or prophylactically, *e.g.*, immediately after birth (Soll and Morley 2001). The new peptide-containing artificial surfactants are now as effective as natural surfactant (Moya et al. 2005; Pfister et al. 2007; Sinha et al. 2005). Early administration of surfactant combined with rapid extubation could be a safe approach (Stevens et al. 2007). It has been proposed to maintain long-term surfactant therapy for prevention of BPD. A pilot trial of this strategy has been performed, but no definitive conclusions can be drawn, and this treatment therefore cannot be recommended at the present time (Laughon et al. 2009).

33.2.4.2.4 Ventilatory Modes

Several approaches have been proposed in order to achieve the goals defined in Sect. 33.2.2.5. Some of them will be discussed below, bearing in mind that new techniques will probably be evaluated over the next few years. The use of *noninvasive ventilation* (or less invasive ventilation) consisting of management by spontaneous breathing with continuous positive airway pressure can prevent or limit the progression of collapse of distal airspaces while avoiding systematic endotracheal intubation. This approach nevertheless requires intubation for administration of exogenous surfactant as prophylaxis or when the diagnosis of RDS is confirmed. Studies performed in the baboon model have demonstrated the efficacy of CPAP to prevent BPD (Thomson 2002; Thomson et al. 2004, 2006). The COIN trial, in which surfactant was not administered systematically, showed a reduction of the “oxygen at 28 days or death” endpoint in the CPAP arm, but did not demonstrate any effect on the “oxygen at 36 weeks or death” endpoint or on the need for oxygen therapy on discharge from hospital (Hascoet et al. 2008; Morley et al. 2008). Other ongoing or finished trials will bring new data to these one.

Nasal intermittent positive pressure ventilation (NIPPV), which can be an alternative to intubation, is discussed elsewhere, and further studies are required to assess its effect on BPD.

Synchronization of the neonate with the ventilator (use of the trigger) represents a definite progress in conventional ventilation, but no published study has demonstrated the value of synchronized ventilatory modes on the incidence of BPD (Greenough et al. 2008). At the very most, the study by Bernstein (Bernstein et al. 1996) reported a significant reduction of the proportion of infants with a birth weight below 1,000 g, oxygen-dependent at 36 weeks (72 % in intermittent mandatory ventilation vs. 47 % in synchronized intermittent mandatory ventilation), demonstrating the value of synchronization. Other ventilatory modes can be proposed, but their efficacy for the prevention of BPD has not yet been demonstrated.

Volume-targeted ventilation, usually not used in the neonatal period has been more studied recently. It is designed to limit volutrauma, which can be achieved in two ways: volume-targeted ventilation in which pressure is controlled and volume-controlled ventilation in which a specific tidal volume is delivered by the ventilator irrespective of the state of lung compliance or the pressure required. Long-term respiratory outcome has been less thoroughly studied with these modes, and it is not possible to conclude on their effect on BPD (Grover and Field 2008; McCallion et al. 2005; Sinha and Donn 2008).

More than 10 years after the first trials of early use of *high-frequency oscillation* (HFO) ventilation in very preterm infants with RDS, it has still not been clearly established whether this technique is able to reduce the rate of long-term respiratory sequelae. The most recent trials compared the results of HFO and conventional mechanical ventilation in 2001 and 2002. The trial performed in France studied infants under the age of 30 weeks with RDS (Morierte et al. 2001). No significant difference was demonstrated in terms of the incidence of BPD. The trial performed in the United Kingdom confirmed this result (Johnson et al. 2002). Only the American study demonstrated a very limited benefit on the BPD rate (Courtney et al. 2002). The Cochrane meta-analysis on this subject indicates a beneficial but limited result (Henderson-Smart et al. 2009), but a careful review of the meta-analysis shows that several parameters were not taken into account which precludes definitive conclusions on this point (van Kaam and Rimensberger 2007).

Permissive hypercapnia, widely proposed in adults for a number of years, can reduce barotrauma and volutrauma, which tend to worsen lung injury. Few randomized trials have been performed and have failed to demonstrate any effect on the incidence of BPD (Woodgate and Davies 2001).

33.2.4.3 Oxygen Administration

Oxygen is a well-known risk factor for subsequent BPD. Initial resuscitation of asphyxial term

infants with room air is as effective as and less harmful than resuscitation with pure oxygen (Saugstad et al. 2008). It is difficult to extrapolate these data to preterm infants which have been less studied (Vento et al. 2009), but, in view of its potential toxicity, the use of oxygen must be closely monitored right from the delivery room.

During hospitalization, supplemental oxygen is obviously necessary. To avoid episodes of hypoxemia and hyperoxia and rapid fluctuations of P_aO_2 , a target O_2 saturation of 85–93 % may decrease the incidence of BPD (Deulofeut et al. 2006, 2007).

33.2.4.4 Anti-inflammatory Agents

33.2.4.4.1 Nonsteroidal Anti-inflammatory Therapy

Pentoxifylline is a phosphodiesterase inhibitor possessing anti-inflammatory properties. It was used in a recent trial of nebulization and appeared to decrease the incidence of BPD. However, this treatment is still at a very preliminary phase of development (Lauterbach et al. 2006).

A more specific approach has been proposed with selective phosphodiesterase inhibitors, which are used in adults for COPD. The results of experimental models appear to be contradictory (de Visser et al. 2008; Mehats et al. 2008).

33.2.4.4.2 Steroid Therapy

As the inflammatory reaction of the lung is probably one of the major factors leading to BPD, it was logical to use corticosteroids, which are powerful anti-inflammatory agents. Three types of steroid regimens were used for at least 20 years: (1) very early treatment during the first 96 h of life followed by rapid reduction; (2) moderately early treatment between the 7th and 14th days of life; and (3) late treatment after the 3rd week of life, generally in infants with persistent ventilatory assistance due to severe BPD. It should be noted that these protocols conducted in the early 1990s very often concerned less preterm populations than those essentially concerned by BPD, with a very low antenatal steroid therapy rate and without the use of surfactant in

some trials. Postnatal dexamethasone reduces mechanical ventilation requirements at 28 days of life and at 36 weeks of corrected age. However, early or moderately early steroid therapy is not accompanied by a reduction of oxygen dependence at term, and none of the three treatment regimens is associated with a reduction of neonatal mortality (Halliday et al. 2003a, b, c). Two more recent meta-analyses of administration of steroids before or after 7 days emphasize that the long-term neurological risks are essentially associated with early steroid therapy, but that the risk of severe retinopathy persists for steroids administered after the first week of life (Halliday et al. 2009a, b).

An attractive approach is that proposed by K. Watterberg for the most preterm infants, which consists of early administration of very low doses of hydrocortisone hemisuccinate designed to prevent the adrenal insufficiency observed at these gestational ages. Unlike the pilot study (Watterberg et al. 1999), the multicenter trial did not demonstrate any efficacy on BPD except in infants born in a context of chorioamnionitis, and this trial had to be interrupted due to an excess of gastrointestinal perforations attributed to the combined use of indomethacin (Watterberg et al. 2004).

An alternative would be the use of inhaled steroids, although they have not been clearly demonstrated to be effective for the prevention of BPD. However, inhaled steroids decrease the duration of mechanical ventilation and reduce the subsequent need for systemic steroids (Shah et al. 2012). Although no serious adverse effects have yet been attributed to inhaled steroids, they must be used very cautiously in view of the experience acquired with systemic steroids.

33.2.4.5 Other Proposed Preventive Treatments

33.2.4.5.1 Nitric Oxide

Apart from its recognized efficacy for the treatment of persistent pulmonary artery hypertension in neonates, NO is one of the promising

strategies for prevention of bronchopulmonary dysplasia (BPD). This choice is based on well-documented pathophysiological mechanisms, especially abnormalities of pulmonary microvascular development during pathological alveolarization and the role of NO in these phenomena. Several experimental studies have provided positive results on alveolarization (Lin et al. 2005; Maniscalco et al. 2002; McCurnin et al. 2005; ter Horst et al. 2007). Finally, several large-scale randomized trials have been published with contradictory results, making it difficult to reach any final conclusions. The meta-analysis on this subject concluded that the use of NO for the prevention of BPD is not currently recommended but could be considered in certain subgroups (Barrington and Finer 2007a, b). Nevertheless, a recent review of these results (Kinsella and Abman 2007) suggests that the effects of inhaled NO are dependent on the time of administration, the dose used, the duration of treatment, the underlying disease and its severity, and the population.

The effects of NO on laboratory parameters and pulmonary function tests were studied in parallel in the clinical trial conducted by Ballard (Ballard et al. 2006). This study demonstrated that NO did not modify the protein and phospholipid composition of surfactant and improved the surfactant properties of tracheal aspirate fluid (Ballard et al. 2007) without modifying markers of inflammation (Truog et al. 2007) and without increasing plasma markers of oxidative stress (Ballard et al. 2008).

A possible treatment for the future could be the administration of angiogenic factors such as VEGF in order to improve pulmonary vasculature (Thebaud et al. 2005).

33.2.4.5.2 Closure of Ductus Arteriosus

Although patent ductus arteriosus is probably associated with BPD (Bancalari et al. 2005), treatment of patent ductus arteriosus, either medical with nonsteroidal anti-inflammatory

drugs such as indomethacin or ibuprofen (Ohlsson et al. 2010) or surgical, has not been clearly demonstrated to be effective in the prevention of BPD. In an experimental model in the baboon, a beneficial effect of ibuprofen therapy was demonstrated on alveolarization (McCurnin et al. 2008), while no such effect was observed after surgical ligation (Chang et al. 2008). However, no clear data are available in human preterm infants (Mosalli and Alfaleh 2008; Raval et al. 2007). Fine characterization of the ductus arteriosus will probably be necessary to predict the efficacy of treatment (McNamara and Sehgal 2007), especially as some authors consider that conservative management comprising fluid restriction and adjustment of ventilation may be sufficient to obtain spontaneous closure of patent ductus arteriosus (Vanhaesebrouck et al. 2007).

33.2.4.5.3 Fluid Restriction and Diuretics

Although the association between BPD and high fluid intake has been reported on several occasions, the efficacy of moderate fluid restriction for prevention of BPD has not been demonstrated, although the meta-analysis on the subject reported a tendency toward reduction (Bell and Acarregui 2008). Diuretics, which improve pulmonary function in dysplastic infants, have also not been shown to be effective when administered early to prevent BPD (Brion and Soll 2008).

33.2.4.5.4 Vitamin A

Retinoic acid is essential in the control of septation (Bourbon et al. 2005), and hyperoxic rat pups treated by retinoic acid may recover normal alveolarization. Vitamin A supplementation has been formally demonstrated to be effective in the prevention of BPD. The Cochrane meta-analysis showed a limited but real benefit in terms of BPD at 28 days and 36 weeks of corrected age, suggesting the value of optimal vitamin A supplementation (Darlow and Graham 2011).

33.2.4.5.5 Caffeine

Caffeine is probably one of the most frequently prescribed treatments in preterm neonates, essentially for the prevention of central apneas. A large-scale international multicenter randomized placebo-controlled study of caffeine included 2,000 infants with a birth weight between 500 and 1,250 g treated with either caffeine citrate or placebo. In the short term (Schmidt et al. 2006), treatment with caffeine was associated with a significant reduction of the duration of tracheal ventilation, noninvasive ventilation, and oxygen therapy (each reduced by about one week). The respiratory benefit was observed on the BPD rate defined at 36 weeks of postmenstrual age (36.3 % in the caffeine group vs. 46.9 % in the placebo group).

Conclusion

Neonatal lung injury leads to BPD which is its main respiratory complication. However, this disease is now dominated more by immaturity than by the consequences of mechanical ventilation. It is therefore very difficult to show that a single and very specific intervention can have a positive effect, which is why, in contrast with clinical experience, some treatments are not found to be effective in randomized trials. Overall management therefore needs to be evaluated globally; a recent study clearly demonstrated the efficacy of multiple interventions (Geary et al. 2008).

Essentials to Remember

- Use quickly optimal CPAP to maintain FRC.
- Limit tidal volumes.
- Limit oxygen delivery.
- Administer surfactant as soon as possible.
- Pay attention to other factors such as nutrition and other preventive agents.

33.3 Ventilator-Associated Lung Injury in the PICU

Thomas Jaecklin and Brian P. Kavanagh

Educational Goals

In this chapter, the reader can learn:

- The definition of ventilator-associated lung injury (VALI), its clinical interface with the acute respiratory distress syndrome (ARDS) and ventilator-induced lung injury (VILI), and its epidemiology
- The main mechanisms by which mechanical ventilation can injure the lung
- The etiology and clinical presentation of ARDS and VALI
- The most frequently used methods to reduce the impact of mechanical ventilation on the lung

33.3.1 Mechanisms of VILI

Many different mechanisms of VILI have been described (Fig. 33.1) and will be discussed with a focus on pediatric patients.

33.3.1.1 Physical Injury

33.3.1.1.1 Baro- and Volutrauma

Initially, air leaks (*i.e.*, accumulation of extra-alveolar air either in the interstitium, mediastinum, pleural cavity, or even the subcutaneous tissue) were the key recognized adverse effect of mechanical ventilation (Pierson 2006). This was thought to be the consequence of mechanical disruption of airspace integrity due to excessive airway pressure (barotrauma). Soon it was observed that large V_T is responsible for the VILI rather than high airway pressures.

To distinguish whether pressure or volume was the injurious agent, a series of studies were undertaken. Rats (Dreyfuss et al. 1988), rabbits (Hernandez et al. 1989), or lambs (Carlton et al. 1990) with healthy lungs were ventilated with

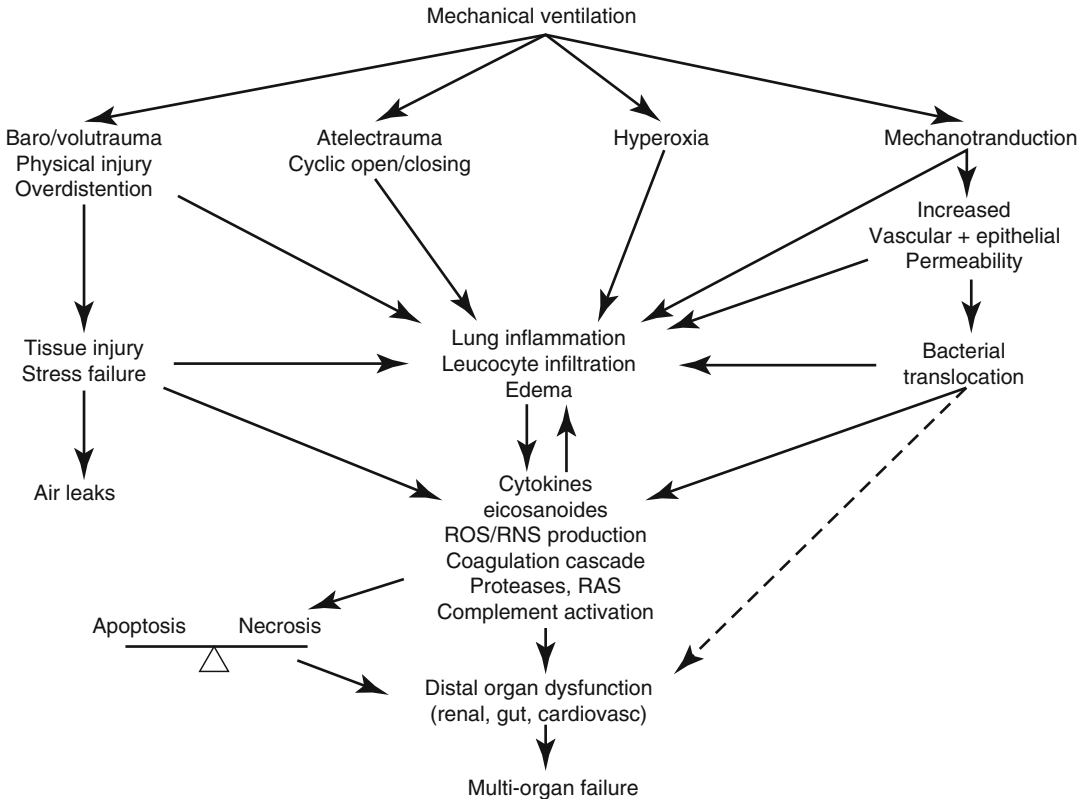


Fig. 33.1 Mechanisms of ventilator-induced lung injury and consequences on other end organs. *ROS/RNS* reactive oxygen/nitrogen species, *RAS* renin-angiotensin system

either high or low V_T , but the peak inspiratory pressures were kept the same by limiting inspiratory thoracoabdominal excursions with straps or casts. In contrast to the animals ventilated with low V_T , those ventilated with high V_T developed pathological and ultrastructural changes of VILI. These ultrastructural changes have been well characterized as tears in the pulmonary endothelium and epithelium due to cellular stress failure (Fu et al. 1992). Whether these lesions at the cellular level are the actual cause of the air leak that can be observed clinically is not established, but the extrapolation is compelling. Nonetheless, these experiments made a strong case that volume, and not pressure, was the main culprit (volutrauma).

The hypothesis that high V_T ventilation is the major contributor to VILI is supported by the findings of a large randomized controlled trial in adults suffering from ARDS, where the mortality

was higher in patients ventilated with a V_T of 12 vs. 6 mL/kg (ARDS Network 2000).

33.3.1.1.2 Atelectrauma

Not only high V_T can induce or worsen lung injury. Mechanical ventilation with low V_T in the absence of PEEP can also lead to lung injury. This was believed to result from cyclic opening and closing (recruitment and de-recruitment) of terminal airspaces (Chu et al. 2004) that lead to lung inflammation and diffuse alveolar damage and was termed atelectrauma. Another possible explanation for this finding was suggested by Mead et al. (1970). Using a mechanical model of interdependent alveoli, he showed that despite a homogeneous transalveolar pressure of 30 cm H_2O , the walls of collapsed alveoli could experience much higher pressures (up to 140 cm H_2O) due to this interdependence. However, in at least one experimental model, the

injury in atelectatic areas is minimal, in contrast to that in the aerated (*i.e.*, nonatelectatic zones) (Tsuchida et al. 2006); in this sense, atelectasis may cause injury by exacerbating the stress in the residual aerated lung.

33.3.1.1.3 Oxygen Toxicity

Another mechanism of physical injury to the lung during mechanical ventilation results from oxygen toxicity. High inspired O₂ concentrations are often required in patients with severe respiratory failure to maintain adequate blood O₂ levels. Nash et al. mechanically ventilated goats with low airway pressures and either room air or 100 % fraction of inspired oxygen (Nash et al. 1971). The hyperoxic animals did not survive more than 4 days on the ventilator, and their lungs showed pathological changes as described above; in contrast, animals breathing room air remained well for up to 2 weeks, and their lung histology was normal. The O₂ toxicity is thought to be mediated through the harmful effect of ROS and peroxidized membrane lipids. Both are produced in excess in the presence of high levels of inspired O₂ (Weinberger et al. 2002). Oxygen levels of 60 % or higher have been consistently shown to induce oxidative stress resulting in inflammation, decreased lung cell proliferation, and altered respiratory mechanics. Especially in children, the histological image is similar to bronchopulmonary dysplasia. The underlying cellular mechanisms for this finding include dysregulated inflammation, altered protease/antiprotease balance, and altered growth or differentiation of lung cells either due to a direct effect of O₂ or due to the harmful compounds mentioned above.

33.3.1.2 Inflammatory Response to Stretch: The Biotrauma Hypothesis

After focusing on the physical effects of mechanical ventilation, it was progressively realized that VILI is an inflammatory disease, largely dependent on neutrophils (Kawano et al. 1987). The exact mechanism by which mechanical ventilation induces this inflammatory process is not clear, but a contemporary theory is the so-called

biotrauma hypothesis (Tremblay and Slutsky 1998), which suggests that mechanical stretch induces the production of inflammatory mediators that contribute to the lung injury and ultimately might lead to multiorgan failure, the primary cause of mortality in patients with severe respiratory failure.

33.3.1.2.1 Inflammatory Cytokines

Evidence supporting the biotrauma hypothesis is largely based on circulating or pulmonary cytokines. It can be expressed as follows: Injurious mechanical ventilation, *i.e.*, high V_T and/or low PEEP, is associated with higher concentrations of inflammatory mediators in human studies (ARDS Network 2000; Ranieri et al. 1999; Stuber et al. 2002) and induces their production in experimental models of VILI in vivo (Wilson et al. 2003) and ex vivo (Tremblay et al. 1997; von Bethmann et al. 1998; Yoshikawa et al. 2004). Cyclic cell stretch in vitro also leads to secretion of cytokines and chemokines (Pugin et al. 1998; Vlahakis et al. 1999). Interventions directed against the production or actions of proinflammatory mediators have been shown to decrease the degree of VILI in experimental studies. Glucocorticosteroids appear to block the proinflammatory nuclear factor κ B (NF- κ B), one of the main proinflammatory transcription factors, and decrease both the level of cytokine mRNA transcription and the degree of lung injury (Held et al. 2001). Several anti-cytokine strategies have led to an improvement of markers of VILI: intratracheal application of polyclonal antitumor necrosis factor- α (TNF- α) antibodies attenuated the impairment of lung compliance, improved histological abnormalities, and reduced leukocyte infiltration after high V_T ventilation (Imai et al. 1999). Systemic anti-macrophage inflammation protein-2 (MIP-2) antibodies reduced the leukocyte migration induced by hyperoxia/hyperventilation (Quinn et al. 2002). Finally, recombinant interleukin-1 (IL-1) receptor antagonists decreased lung injury and leukocyte infiltration (Narimanbekov and Rozycki 1995).

It is important to recognize that causation has not yet been proved in any of the foregoing. As well, some of the experimental data suggest that

the link between proinflammatory mediators and VILI might not be a simple “cause and effect” relationship. For example, some groups were unable to detect increases in inflammatory mediators, in particular TNF- α , using in vivo and in vitro models of VILI (Haitsma et al. 2000; Ricard et al. 2001; Verbrugge et al. 1999). Quinn et al. documented unchanged chemokine concentrations and neutrophil recruitment despite the induction of significant lung edema after 2 h in a rat model of high V_T injury (Quinn et al. 2002). Also the administration of aerosolized recombinant TNF- α and interferon- γ to spontaneously breathing rats modulated the function of pulmonary and systemic monocytes, but led to only minimal pulmonary edema and inflammation (Debs et al. 1988), suggesting that these mediators are not pathogenic per se. Finally, Wrigge et al. ventilated 39 healthy patients scheduled for elective surgery under general anesthesia during 1 h with parameters that are generally considered injurious (V_T 15 mL/kg without PEEP) vs. a so-called protective ventilation strategy (V_T 6 mL/kg, PEEP of 10 cm H₂O) and detected no difference in plasma cytokine levels between the two groups (Wrigge et al. 2000). Finally, mediators other than cytokines have also been investigated as potentially pathogenic in the context of VILI.

33.3.1.2.2 Coagulation Factors

Intra-alveolar fibrin is common in injured lungs, and this observation has preceded the discovery of “cross talk” among inflammatory mediators and the coagulation cascade during lung injury (Schultz et al. 2006). Proinflammatory mediators can stimulate the expression of tissue factor, thereby activating coagulation (van der Poll et al. 2001), and can suppress activation of protein C and promote the secretion of thrombomodulin and plasminogen activator inhibitor-1 (PAI-1). Increased levels of thrombomodulin and PAI-1, with reciprocal decreases in activated protein C (APC), exist in patients with ARDS and correlate with outcome (Ware et al. 2006). Finally, injurious ventilation is associated with similar perturbations (Dahlem et al. 2005), whereas protective ventilation may atten-

uate coagulation activation and prevent inhibition of fibrinolysis (Ware et al. 2006; Choi et al. 2006).

Because of these associations, components of the coagulation system have been identified as potential therapeutic targets. Heparin, initially promising because of anti-inflammatory as well as anticoagulant properties (Hochart et al. 2006), has little net benefit in the clinical setting (MacLaren and Stringer 2007). Other interventions have been disappointing also: Tissue factor pathway inhibitor (tifacogin) did not attenuate lung injury in a clinical trial (Abraham et al. 2003), and APC – does not improve outcome in patients with lung injury (Liu et al. 2008) despite its anti-inflammatory, antiapoptotic, and anticoagulation activity. Finally, thrombomodulin, an important cofactor in fibrin formation and activation of protein C, has a complex relationship with lung injury and is being evaluated as a potential therapeutic target (MacLaren and Stringer 2007; Ware et al. 2003).

33.3.1.2.3 Hormones

A prototypic hormone related to lung injury is angiotensin II. This hormone increases tissue vascular permeability via the production of eicosanoids and vascular endothelial growth factor as well as by alteration of cytoskeletal proteins (Suzuki et al. 2003). In addition, by enhancing intercellular adhesion and chemokine expression, angiotensin II augments migration of inflammatory cells and promotes tissue repair (Suzuki et al. 2003). Several effects point to a potential role in VILI. *First*, high V_T upregulates important components of the renin-angiotensin system and increases expression of angiotensin receptors (Jerng et al. 2007). *Second*, the genotype (*i.e.*, DD) coding for more active angiotensin-converting enzyme (ACE) is more prevalent in critically ill patients who have ARDS (*vs.* those who do not); and, among those with ARDS, the DD genotype is associated with higher mortality (Marshall et al. 2002). *Third*, pretreatment with the ACE inhibitor captopril (or the angiotensin II receptor antagonist, losartan) attenuates VILI in vivo (Jerng et al. 2007). Finally, ACE-2 is a captopril-insensitive ACE homolog that inactivates

angiotensin II; it protects against experimental lung injury (Imai et al. 2005). Thus, circulating angiotensin II represents a candidate mediator. However, research continues to better understand the complex renin-angiotensin system. For example, several angiotensin II receptors have been described, and while one receptor type (AT₁a) promotes lung injury, another (AT₂) appears to protect (Imai et al. 2005).

33.3.1.2.4 Lipid-Derived Mediators

Levels of eicosanoids and platelet-activating factor (PAF) correlate with lung injury in several animal models of VILI (Goggel and Uhlig 2005; Miyahara et al. 2008). These molecules are potent modulators of vascular tone, permeability, inflammation, and platelet activation. They form a complex network, however, and may have pro-inflammatory or anti-inflammatory activity depending on the context. Inhibition of the proximal regulatory enzyme (cytosolic phospholipase A2; cPLA2) attenuates capillary permeability induced by high V_T (Miyahara et al. 2008); and inhibition of all downstream enzymes (*i.e.*, cyclooxygenase, lipoxygenase, and cytochrome P450) is required for effective protection, suggesting complex overlapping function (Miyahara et al. 2008). Another important candidate lipid mediator is PAF, which increases platelet activation, leukocyte attraction, and microvascular permeability, in part via increasing intracellular Ca^{2+} , and in part via synthesis of prostaglandins and ceramides (Goggel et al. 2002). Earlier preclinical inhibition of the PAF receptor was effective (Nagase et al. 1999), but clinical trials did not demonstrate an impact on mortality (Johnson et al. 2001). Ceramides (and other sphingolipids, *e.g.*, sphingosine-1-phosphate and sphingomyelin) have recently been recognized as potentially important in VILI (Uhlig and Gulbins 2008), regulating apoptosis and integrity of intercellular junctions. Increased acid sphingomyelinase activity (resulting in elevated ceramide levels) occurs in the lungs of patients with ARDS (Rauvala and Hallman 1984), and in sepsis, the circulating levels correlate with mortality (Claus et al. 2005; Drobnik et al. 2003). Finally, inhibition of acid sphingomyelinase stabilizes

surfactant (von Bismarck et al. 2008) and attenuates pulmonary inflammation in *in vivo* lung injury (Uhlig and Gulbins 2008).

33.3.1.2.5 Oxidants

Circulating reactive oxygen (or nitrogen)-derived species are present in patients with acute lung injury (ALI; (Zhu et al. 2001)) and might affect previously healthy lung regions or systemic organs. This field is complex, but pharmacologic inhibition and genetic modification of enzymes that produce ROS has attenuated VILI in experimental settings (Abdulnour et al. 2006).

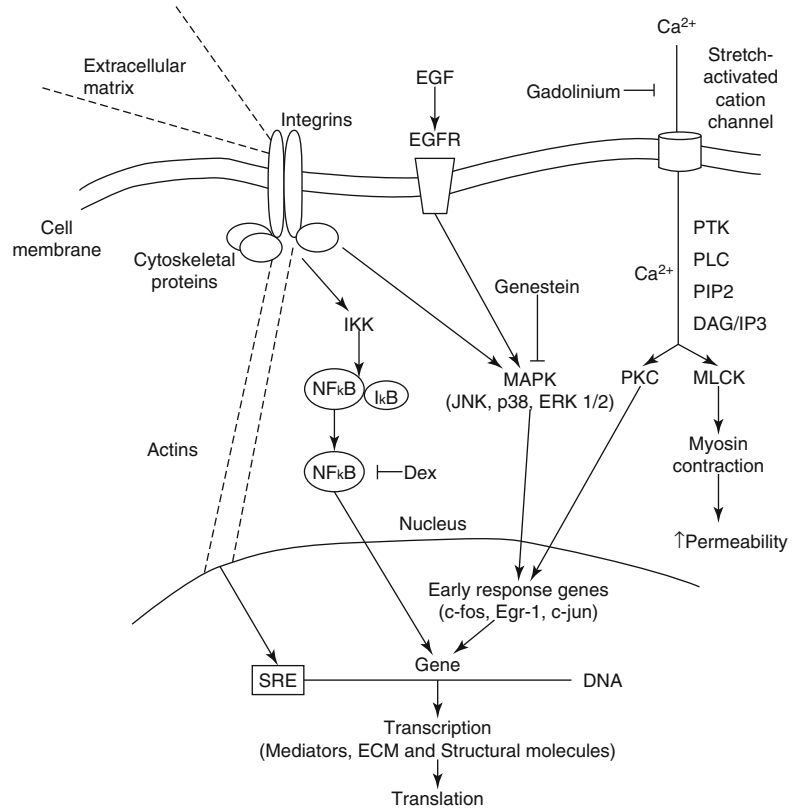
Injurious mechanical ventilation undoubtedly causes pulmonary inflammation. Whether this inflammation represents a “healing” response to alveolar-capillary injury (Fu et al. 1992) or whether the secreted cytokines initiate (or potentiate) the injury is unknown. Cytokines might be innocent bystanders, biological markers, or causative factors of VILI, and mediators other than cytokines might be responsible for the lung injury. Despite strong supportive evidence of association, definitive proof of cause and effect for the biotrauma hypothesis is still lacking.

33.3.1.3 Cellular and Matrix Response to Stress

In recent years, evidence on intracellular mechanisms of VILI has mushroomed. Mechanotransduction, the sensing of mechanical stress at the cellular level and its transformation into an intracellular signal, seems to be an active process as opposed to the passive physical injury described in earlier studies. Several mechanisms have been proposed (Fig. 33.2).

First, mechanical stress can lead to an autocrine secretion and binding of epidermal growth factor family ligands that activate intracellular signaling cascades (Tschumperlin et al. 2004). *Second* is the sensing of physical forces by stretch-activated cation channels, which allow Ca^{2+} to enter the cell upon cell stretch. Such increased intracellular Ca^{2+} concentration activates myosin light-chain kinases, which phosphorylate myosin and cause cellular contraction and increased intercellular permeability

Fig. 33.2 Schematic of intracellular pathways activated by mechanical stretch of the cell membrane. *IKK* inhibitor of NF κ B kinase, *NF κ B* nuclear factor κ B, *I κ B* inhibitor of NF κ B, *Dex* dexamethasone, *SRE* stretch response promoter element, *EGF* epidermal growth factor, *EGFR* EGF receptor, *MAPK* mitogen-activated protein kinases, *JNK* c-jun N-terminal kinase, *ERK* extracellular signal-related kinase, *PKC* protein kinase C, *PTK* phosphotyrosine kinase, *PLC* phospholipase C, *PIP2* phosphatidylinositol-diphosphate, *DAG* diacylglycerol, *IP3* inositoltriphosphate, *MLC* myosin light-chain kinases, *ECM* extracellular matrix (Adapted from Vlahakis and Hubmayr (2003))



(Parker et al. 1998). Other components of the signaling cascade including protein kinase C, early response genes (c-fos, c-jun, Egr-1), and NF- κ B can also be activated by the rise in intracellular Ca^{2+} (Vlahakis and Hubmayr 2003). These molecules have been associated with increased production of proinflammatory cytokines (Tremblay et al. 1997; Held et al. 2001). *Third*, there are physical connections between the extracellular matrix and the nucleus consisting of the integrins (transmembrane proteins) and the cytoskeleton (intracellular scaffolding) (Vlahakis and Hubmayr 2003). These structures are thought to play a role in sensing, transducing, but also regulating deforming stress. Stretch leads to the activation of mitogen-activated protein kinases (MAPK), with its three major signaling components c-Jun N-terminal kinase, p38, and extracellular signal-related kinase 1 and 2 (ERK 1 and 2) through the stimulation of integrins but also through the activation of membrane receptors (e.g., epidermal growth factor receptor). Each of

the three subunits can lead to the phosphorylation of activating protein-1 (AP-1), which promotes the transcription of cytokines, adhesion molecules, and other stretch-related gene products (Oudin and Pugin 2002).

These multiple pathways converge in the activation of early response genes (e.g., c-fos, c-jun, Egr-1), which encode proteins related to transcriptional factors and signal transduction (Liu et al. 1999). The first in vivo study of the effect of VILI on gene activation identified several genes (e.g., Egr-1) that were upregulated by high V_T , as well as several others that were downregulated (Copland et al. 2003). Indeed one of the identified genes, Egr-1 (early growth response factor-1 (Ngiam et al. 2007)), has now been shown to be induced by high V_T and to induce injury by increasing the transcription of prostanoid enzymes (Ngiam et al. 2010). Thus, stretch-induced activation of genes can ultimately stimulate the transcription and translation of cytokines, growth factors, extracellular matrix,

structural proteins, and others as an adaptive response to mechanical stretch.

Mechanical strain can also modulate protein synthesis or secretion at the posttranscriptional level as shown by the ongoing stretch-related synthesis of fibronectin despite the presence of actinomycin D, an inhibitor of transcription, and the increased secretion of proteinoglycans and glycosaminoglycans following stretch (Mourgeon et al. 1999; Xu et al. 1996). Another pathway implicated in intracellular signaling in VILI is the phosphoinositide 3-kinase- γ (PI3K γ) pathway (Lionetti et al. 2006). The PI3K γ is a G-protein-sensitive enzyme that regulates inflammation and cell survival. PI3K $\gamma^{-/-}$ transgenic mice had better lung compliance, fewer hyaline membranes, and less epithelial detachments after high-stretch ventilation than wild-type mice, despite similar proinflammatory cytokine levels and I κ B phosphorylation (NF κ B inhibitor). These knockout mice showed increased apoptosis in the lung, whereas wild-type mice showed increased cell necrosis (Lionetti et al. 2006). This study suggests that high-stretch ventilation directly triggers a PI3K γ -mediated cascade that leads to an antiapoptotic/pro-necrotic cell death signal. However, the regulation of apoptosis is complex, and inflammatory mediators seem to contribute to its regulation in a predominant fashion (Papathanassoglou et al. 2000).

33.3.2 Clinical Presentation

Ventilator-associated lung injury shares most clinical features with and is – discussed above – often indistinguishable from ARDS. Ventilator-induced lung injury can be suspected where obvious “barotrauma” (lung cysts or air leaks) develops after commencing mechanical ventilation. Alternatively, worsening injury with the use of injurious ventilation parameters (*i.e.*, low or absent PEEP and/or high V_T) may give rise to suspicion. However, the ventilation parameters that are injurious or potentially harmful are not consistent among all patients (Deans et al. 2005).

The 1994 American-European Consensus Conference defined ALI and its more severe

Table 33.1 The European-American Consensus Conference definition of ARDS and ALI

Acute onset
Bilateral infiltrates on chest radiography
Pulmonary-artery wedge pressure of ≤ 18 mmHg or absence of clinical evidence of left atrial hypertension
Acute lung injury considered to be present if $P_aO_2:FiO_2$ is ≤ 300
Acute respiratory distress syndrome considered to be present if $P_aO_2:FiO_2$ is ≤ 200

ARDS acute respiratory distress syndrome, ALI acute lung injury, P_aO_2 partial pressure of arterial oxygen, FiO_2 fraction of inspired oxygen

manifestation ARDS by the presence of four criteria (Table 33.1, Bernard et al. 1994). This is a purely clinical definition that is easy to apply at the bedside but that does not account for the etiology, the severity (*i.e.*, organ involvement other than the lung), or prognosis of the illness. Traditionally, three stages of disease progression were identified (Ware and Matthay 2000).

The acute or exudative phase is manifested by the rapid onset of respiratory failure in a child with risk factors for the condition. Arterial hypoxemia that is refractory to the treatment with supplemental oxygen is a characteristic feature. There are bilateral diffuse or patchy lung infiltrates on chest radiograph that vary in density, and pleural effusion might be present. Computed tomography demonstrates heterogeneity of lung involvement with alveolar filling, consolidation, and atelectasis predominantly in dependent lung zones, whereas other areas may be relatively spared. Pathological findings include diffuse alveolar damage, with infiltration of neutrophils and macrophages, extravasation of erythrocytes, and formation of hyaline membranes (fibrin deposits along the alveolar lining), protein-rich edema fluid in the alveolar spaces, as well as disruption of the capillaries and alveolar epithelium (see Figure 1-4 in Ware and Matthay (2000)).

The acute phase can resolve completely or progress to *the fibrotic phase*, which is characterized by a fibrosing alveolitis with persistent hypoxemia, increased alveolar dead space, and a further decrease in pulmonary compliance. Pulmonary hypertension, owing to obliteration of the pulmonary capillary bed, may – in rare

cases – be severe and can lead to right ventricular failure. Chest radiographs show linear opacities, consistent with the presence of evolving fibrosis. Pneumothorax may occur, and computed tomography of the chest shows diffuse interstitial opacities and bullae. Histologically, there is fibrosis along with acute and chronic inflammatory cells and partial resolution of the pulmonary edema.

Ultimately, *the recovery phase* is characterized by the gradual resolution of hypoxemia and improved lung compliance. Typically, the radiographic abnormalities and pulmonary function return to normal, but defect healing with various degrees of lung fibrosis that impacts on the long-term pulmonary function and growth of the patient may occur (Ware and Matthay 2000).

33.3.3 Etiology and Predisposing Factors

Acute lung injury or ARDS can develop from direct injury to the lung or occur after injury to another organ. Table 33.2 lists the most common causes.

Whereas the etiology of ALI is similar in adults and children, predisposing factors and comorbidities vary according to age groups. Infants (and preterm infants or patients with

intrauterine growth retardation in particular) may be additionally susceptible because of surfactant deficiency, immaturity of the lung and immune system, and because of comorbidities that often require aggressive therapy (*e.g.*, primary respiratory failure, congenital heart disease, pulmonary hemorrhage, sepsis) (Attar and Donn 2002).

Additional issues may complicate this situation. ARDS is a heterogeneous disease impairing some lung regions and leaving others unaffected. These latter portions have a normal compliance and receive the entire V_T applied by the mechanical ventilator. These small, unaffected portions have been termed “baby lung” by adult clinicians (Gattinoni and Pesenti 2005). Because the infant respiratory distress syndrome also leads to patchy involvement of the lung, the “baby lung” of a newborn is extremely small and therefore easily overdistended and injured.

The antioxidant system of preterm infants is immature which results in an increased susceptibility to the overproduction of ROS induced by the supplemental oxygen therapy often needed in this patient population. Finally, increased chest wall compliance may make the lungs more prone to iatrogenic overdistention.

More recently, genetic predispositions for ALI/ARDS were recognized. Certain genotypes for a wide array of factors including IL-6, IL-10, TNF- α , vascular endothelial growth factor, ACE, surfactant proteins, immune receptors, or transcription regulators (*e.g.*, NF- κ B) were associated with increased (or reduced) susceptibility for ARDS and mortality thereof (Gao and Barnes 2009). There are hopes that genotyping will ultimately allow the study of more homogeneous patient groups in clinical trials, as heterogeneity of study populations is thought to be one of the main reasons for the lack of positive evidence for any treatment modality in ALI/ARDS. Patient stratification might allow to determine more accurate prognostic factors and guide the clinician in the difficult task of tailoring the various treatment options to every individual patient. In addition, better understanding of the biochemical basis for VALI may lead to therapies that could have a role in preventing ventilator-associated injury in many patients – whether genetically susceptible or not.

Table 33.2 Common etiologies of ARDS/ALI

Direct lung injury	Indirect lung injury
Sepsis (pulmonary)	Sepsis (other source)
Pneumonia	Severe trauma
Broncho-aspiration	Shock
Near drowning	Transfusion of blood products (TRALI)
Pulmonary contusion	Cardiopulmonary bypass or ECMO
Inhalation injury	Intoxication
Reperfusion injury after lung transplant	Hepatic failure, pancreatitis
Fat embolism	Severe burns
Injurious mechanical ventilation (VALI)	No comorbidity

Adapted from Rubenfeld et al. (2005), Ware and Matthay (2000)

ARDS acute respiratory distress syndrome, ALI acute lung injury, TRALI transfusion-related acute lung injury, ECMO extracorporeal membrane oxygenation, VALI ventilator-associated lung injury

33.3.4 Prevention and Management of VILI

The clinician has a restricted therapeutic armamentarium to prevent or treat ARDS and VALI. Strong evidence for most treatment modalities is lacking, and none of them (apart from avoiding high V_T) has shown a mortality benefit in clinical trials. Nevertheless, several of these therapeutic measures might be considered protective or therapeutic because they have shown to affect surrogate measures of lung injury (*e.g.*, levels of circulating inflammatory mediators, histology) or secondary outcome measures (*e.g.*, ventilator-free days, hospital or intensive care unit length of stay). Based on what was discussed above (see Sect. 33.3.1), the aim of any intervention in patients with ARDS should be the reduction of pulmonary overdistention, minimization of atelectasis, and attenuation of lung inflammation whether caused by the underlying disease process or by mechanical ventilation. The most established of these therapies are discussed below.

33.3.4.1 Conventional Mechanical Ventilation

33.3.4.1.1 Low Tidal Volume

Two large randomized trials have shown that avoidance of high V_T (6 vs. 12 mL/kg) reduced mortality in patients with ARDS (ARDS Network 2000; Amato et al. 1998). Some aspects of these trials, especially the control treatment, have complicated precise interpretation of the studies (Deans et al. 2005; Eichacker et al. 2002). Nonetheless, it is generally accepted (and supported by a large amount of experimental evidence) that high V_T is harmful, at least in patients with lung disease.

33.3.4.1.2 Limiting Airway Pressure

The American-European Consensus Conference on ARDS recommends minimizing peak inspiratory pressure (PIP) by using strategies that sometimes result in permissive hypercapnia (see below) and the use of pressure-controlled or pressure-limited, volume-cycled (also called volume-guaranteed) ventilation (Artigas et al. 1998).

A safe recommended pressure limit is supported by the ARDS-network randomized clinical trial comparing high vs. low V_T in ARDS patients (ARDS Network 2000) and by meta-analysis of all of the outcome-based V_T trials (Eichacker et al. 2002).

33.3.4.1.3 Oxygen

High levels of inspired O_2 can lead to levels of ROS that exceed the body's antioxidant capacities. ROS that are not neutralized can lead to lung injury by inducing lipid peroxidation, DNA damage, and protein oxidation. These effects can be observed in any organ, but the lung is particularly susceptible because it is in direct contact with molecular O_2 . As is the case for V_T or airway pressures, a generalizable precise limit for FiO_2 may not be possible. Most clinicians believe that high levels of inspired oxygen should be used for as short a period as possible, especially where FiO_2 exceeds 0.65. Newborns, and preterm infants in particular, are at greater risk for oxygen toxicity than older children and adults because of their immature antioxidant defenses; lower FiO_2 targets should be considered in this age group.

33.3.4.1.4 Positive End-Expiratory Pressure

A vast body of experimental evidence shows that mechanical ventilation without PEEP can worsen or induce lung injury (Muscedere et al. 1994; Dreyfuss and Saumon 1998). Three large randomized controlled clinical trials have assessed clinical outcomes of high vs. low PEEP levels in patients with ALI or ARDS (Meade et al. 2008; Brower et al. 2004; Mercat et al. 2008). None of them showed a reduction in mortality by the use of higher levels of PEEP. However, two studies demonstrated improvement of secondary outcome measures including ventilator – and organ failure – free days, lung compliance, hypoxemia, and the use of adjunctive or rescue therapies and fluid requirements with similar rates of side effects. The indication of PEEP during conventional mechanical ventilation, even in healthy individuals, is currently undisputed. However, it is possible that the three trials gave a neutral

result because there was no attempt to differentiate those who might benefit from elevated PEEP (*e.g.*, with increased compliance) *vs.* those whom elevated PEEP might harm. Thus, the level of PEEP has to be individualized to each patient and depends on the respiratory mechanics (compliance and resistance of the entire respiratory system), comorbidities (*e.g.*, abdominal distention, fluid overload, capillary leak), and response to recruitment maneuvers. Lung recruitment and assessment of appropriate lung volumes are discussed elsewhere in this textbook.

33.3.4.1.5 The “Baby Lung”

In 2005 Gattinoni et al. proposed the concept of “baby lung” following the observation in computer tomography studies in adult patients with ARDS that only a small proportion of lung is aerated (Gattinoni and Pesenti 2005). In these patients, the normally aerated proportion of the lung corresponds to 300–500 g of lung tissue, which is about the lung volume of a 5- to 6-year-old child. This volume is obviously smaller with very younger children. These authors therefore suggested that the injured lung is not actually “stiff” but instead “small” (they called it the “baby lung”) and that it is a functional – not an anatomical – entity. This fact has to be taken into consideration when parameters for mechanical ventilation are chosen in a patient with ARDS/ALI or VALI. Ventilating these patients with parameters based on body weight or theoretical principles will result in VALI (*i.e.*, overdistention and subsequent injury) of the remaining healthy part of the lung. In general the following principle applies: the sicker the lung, the smaller the “baby lung” is, and therefore the greater the potential for VALI. In these patients, it is critical to repeatedly consider the ideal FiO_2 , V_T , PEEP, and plateau pressures, as well as the implications of permissive hypercapnia, and the potential role adjuncts to conventional ventilation (prone positioning, inhaled nitric oxide) and the use of high-frequency oscillation ventilation or extracorporeal technology.

33.3.4.2 High-Frequency Oscillation Ventilation

This topic is discussed in detail elsewhere in this book. Briefly, high-frequency oscillation ventilation (HFOV) moves volumes below the dead space of the patients at high frequencies (8–15 Hz) with an active inspiration and expiration and uses a constant distending pressure. Gas exchange occurs via convective mechanisms as well as by diffusion. Recruitment and CO_2 clearance are therefore managed independently by the mean airway pressure and the delivered V_T (increased with rising pressure amplitude and lowered frequency), respectively. In theory, this mode of ventilation is lung protective because it avoids the large pressure swings of conventional ventilation and may minimize atelectasis. The risk for overdistention and barotrauma remains. HFOV has been studied in the neonatal population, but results of clinical trials are equivocal (Courtney et al. 2002; Johnson et al. 2002; Rimensberger et al. 2000; Bollen et al. 2005). Variations in the ventilation strategies between the studies likely explain the differences in the study findings, as does the changing nature of what has been termed “conventional” (or “traditional”) ventilation as control groups for studies of HFOV (Bollen et al. 2007; van Kaam and Rimensberger 2007).

33.3.4.3 Permissive Hypercapnia

This topic is discussed in detail in Chaps. 26 and 27.

33.3.4.4 Pharmacologic Intervention

Aside from steroids for preterm lung development (discussed elsewhere in this book), no other pharmacologic therapy has yet proven to be beneficial in the context of ARDS, ALI, or VALI. Several drugs, for example, heparin (MacLaren and Stringer 2007), tissue factor pathway inhibitor (tifacogin) (Abraham et al. 2003), and APC (Liu et al. 2008), have undergone clinical testing but have not improved mortality or lung injury. Specific mediator-directed approaches have also been negative.

33.3.5 VILI in the Future

Ideally, we would better be able to understand the bedside physiology, preferably using noninvasive technology, and therefore titrate the mechanical ventilation to suit each patient's lungs at each phase in their illness. Beyond that, there are additional opportunities. First, we would know the absolute local O₂ requirements for the most vulnerable tissues in any critically ill patients, enabling the clinician to decide on whether maximal oxygenation was necessary, or whether a degree (and to what extent) permissive hypoxemia might be titrated. Second, we would understand how ventilation injures lungs (and worsens outcome), and for any "necessary" burden of mechanical ventilation (that has been optimized to minimally injure), we could treat a patient with a specific pathway inhibitor or activator that would bypass the biochemical mechanism whereby the ventilator was causing residual injury. Such approaches would be optimal in individuals that are genetically susceptible to ventilator-associated lung injury.

Essentials to Remember

- VALI is an adverse effect of mechanical ventilation and can contribute to a patient's pulmonary morbidity and multiorgan failure.
- VALI is an inflammatory disease with mechanical (volu-, baro-, atelectrauma, hyperoxia), humoral (biotrauma), and cellular (mechanotransduction) triggers.
- Clinically, there are three distinct phases (exudative, fibrotic, and recovery); primary pulmonary insults can be distinguished from secondary forms with respect to etiology.
- Several methods can effectively reduce the degree of VALI, like permissive hypercapnia, protective conventional ventilation (with low V_T , PEEP, and an open lung strategy), high-frequency ventilation, and steroid treatment.

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Pierre-Henri Jarreau

Educational Aims

- Understanding pathophysiology and risk factors of gross air leaks during mechanical ventilation
- Preventing air leaks by fine adaptation of mechanical ventilation
- Evaluating treatment options

Air leaks, including pulmonary interstitial emphysema (PIE), pneumothorax, pneumomediastinum, pneumopericardium, subcutaneous emphysema, pneumoperitoneum, and systemic air embolism, constitute a major cause of morbidity and mortality. For example, PIE is associated with a sixfold higher mortality in very low birth weight (VLBW) infants. Air leaks result from alveolar or small airway rupture, leading to the presence of air in structures in which air is not normally present. Overdistension of the alveoli, leading to alveolar rupture, may be spontaneous or due to mechanical ventilation. The incidence of these air leaks in the neonatal intensive care unit (NICU) has dramatically decreased with improvement of respiratory care.

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Among the various types of air leaks, only pneumothorax and pneumopericardium, and sometimes pneumomediastinum and pneumoperitoneum, may require emergency intervention to restore respiratory function. Pulmonary emphysema is very difficult to treat, although some treatments have been proposed.

Prevention is the best way to avoid air leaks, firstly by decreasing inflation pressure.

34.1 Pathophysiologic Mechanisms of Airway and Alveolar Rupture

34.1.1 Pathophysiology

The first description of air leak from the alveoli in an overdistended lung is old ((Macklin 1939), cited in (Korones 2003)). Air leaks result from high intra-alveolar pressure due more frequently to mechanically applied pressure (insufflation), retention of large volumes of gas, and uneven ventilation, leading to rupture of the small airways or alveoli. In particular circumstances, such as meconium aspiration syndrome, but also during the first normal breaths, as there is an uneven distribution of air in the lung (and possibly atelectasis), some alveoli are overdistended during inspiration with high transpulmonary pressure, and therefore air leaks can occur during the first spontaneous breaths (Chernick and Avery 1963).

An animal model of respiratory distress syndrome (RDS) has demonstrated that, in immature

lungs, which are stiff because of surfactant deficiency, ruptures tend to occur in small terminal airways rather than in distal saccules (Ackerman et al. 1984). Moreover, the number of interalveolar connections (pores of Kohn) is decreased in immature lungs, which increases uneven ventilation (Greenough 2003).

Air leaks can be trapped in connective tissue sheaths, leading to PIE, or can dissect these sheaths towards the hilum and may then enter the mediastinum via peribronchiolar and perivascular spaces. Air bubbles can be trapped in the mediastinum, leading to pneumomediastinum, or rupture can occur, creating pneumothorax or pneumopericardium. Pneumoperitoneum is due to extension of mediastinal air along the great vessels and esophagus into the retroperitoneal space and then in the intraperitoneal cavity after rupture of the posterior peritoneum. From the peritoneum, air may spread to the scrotum (pneumoscrutum) probably after migration through the processus vaginalis.

Air can also enter subcutaneous tissues (subcutaneous emphysema), but this can also be due to trauma induced by respiratory care (Markus-Rodden et al. 2008).

One of the fatal consequences of air leaks is air embolism (Lee and Tanswell 1989; Beluffi and Perotti 2009) due to very high insufflation pressures in assisted ventilation, particularly in infants with extremely stiff lungs. Air is injected directly into the blood vessels or via dissection of pulmonary vein sheaths or may enter the systemic circulation via the lymphatics (Booth et al. 1995). Air embolism can also result from traumatic procedures or alveolar capillary fistula.

The type of pulmonary air leak depends on the ability of gas to travel in connective tissue. As connective tissue is more extensive in immature lungs, PIE is more likely to occur in these patients than pneumothorax (Greenough 2003).

34.1.2 Consequences of Air Leaks

PIE may be the first sign of air leaks, mainly occurring in babies with the most immature lungs, and can have very serious consequences, even if it does not evolve towards other forms. Air enters and

accumulates in connective tissue sheaths possibly resulting in a vicious cycle: PIE increases the gas volume in the lung and consequently decreases lung compliance (Hansen et al. 2005) and, as air accumulates in connective tissue sheaths and lung lymphatics (Boothroyd and Barson 1988), it compresses airways and increases airway resistance. It may compress the adjacent lung, creating atelectasis. CO₂ retention and oxygen requirements consequently increase, leading to an increase of inflation pressure which in turn aggravates PIE. Two forms of PIE are usually described (Miller et al. 2006): a diffuse form observed in very young infants, often associated with prolonged ventilation and closely correlated with bronchopulmonary dysplasia (Gaylord et al. 1985), and a localized form. Experience shows that spontaneous or induced evolution of PIE towards pneumothorax may lead to improvement of the clinical situation.

The consequences of pneumomediastinum are due to accumulation of air which can rarely lead to tension that may compromise circulation (Hansen et al. 2005) or respiration by compression of the main bronchi.

Pneumothorax may collapse the lung or shift the mediastinum, resulting in immediate asphyxia, sometimes associated with circulatory collapse due to compromise of venous return. Hypoxemia results from decreased alveolar ventilation and right-to-left shunting through atelectatic areas.

Pneumopericardium impairs atrial and ventricular filling and, in the most severe forms, may decrease cardiac output, leading to systemic collapse. The mortality rate can be very high, especially when pneumopericardium is not recognized and rapidly treated (Reppert and Ment 1977).

Pneumoperitoneum may compromise respiration by impeding diaphragmatic course or circulation by compression of the inferior vena cava (Korones 2003).

Air embolism is nearly always fatal.

34.2 Incidence and Risk Factors

Apart from spontaneous pneumothorax, risk factors are linked to underlying disease, term, and birth weight and to the type of mechanical

ventilation (including vigorous resuscitation at birth) and sometimes by specific procedures (chest drainage through a needle, insertion of intravenous catheters).

In older reports (Yu et al. 1986), 2–8 % of infants admitted to the NICU presented air leaks, but the incidence was higher in VLBW infants. Madansky et al. reported the data from 11 studies and showed that air leak occurred in 12 % of infants with RDS not mechanically ventilated, 11 % of infants spontaneously breathing under CPAP, and 26 % of infants on mechanical ventilation (Madansky et al. 1979).

Pulmonary interstitial emphysema essentially, if not exclusively, occurs in preterm infants with immature lungs, usually after mechanical ventilation, but sometimes without mechanical ventilation (Greenough et al. 1984; Berk and Varich 2005). Incorrect positioning of endotracheal tube may be responsible for localized PIE (Greenough et al. 1984; Thayyil et al. 2008). Recently, Verma et al. looked for risk factors in 45 extremely low birth weight infants and demonstrated that infants with PIE had lower Apgar scores, increased surfactant administration, higher maximum inspired oxygen concentration, and higher mean airway pressure during the first week of life. Surprisingly, the dose of magnesium sulfate received antenatally appeared to be an independent risk factor (Verma et al. 2006).

Spontaneous pneumothorax and pneumomediastinum occur in about 1–2 % of all live births, but very few are symptomatic, as symptomatic pneumothorax seems to be present in only 0.05–0.07 % of live births (Korones 2003). Postmaturity may be a risk factor (Chernick and Avery 1963). These conditions are likely caused by the high transpulmonary pressures generated by the first breaths.

In the majority of cases, air leaks occur in a context of underlying disease, predominantly RDS, meconium aspiration syndrome, and pulmonary hypoplasia (Miller and Carlo 2008). In the Vermont Oxford database, the incidence of pneumothorax in infants weighing less than 1,500 g was 8.6 % in 1991 and 7.3 % in 1999 (Horbar et al. 2002). In the National Institute of Child Health and Development (NICHD) neonatal

network, the incidence of pneumothorax between 1990 and 2002 was 13 % in infants weighing less than 750 g and 3 % in infants between 1,000 and 1,250 g (Fanaroff et al. 2007).

The mode of mechanical ventilation and respiratory care is also important.

Recently, Klinger et al. reported that 74 out of 679 VLBW infants admitted to the NICU developed pneumothorax. After adjustment, multivariate analysis showed that an increased risk of pneumothorax was associated with maximal peak inspiratory pressure, minimal FiO_2 , pulmonary hemorrhage, and maximal arterial CO_2 . A decreased risk was associated with maximal positive end-expiratory pressure. All these factors were present on the day of pneumothorax and neither initial ventilatory variables nor initial severity of the disease appeared statistically significant (Klinger et al. 2008). The number of suction procedures also appears to be important. This study emphasized the importance of careful control of mechanical ventilation and optimizing lung recruitment with PEEP. This must be performed cautiously, as a meta-analysis on continuous distending pressure showed an increased risk of pneumothorax, but it included four old trials (Ho et al. 2000). Notably, the increased incidence of pneumothorax observed in the continuous positive airway pressure (CPAP) group in the COIN trial emphasizes the fact that optimal PEEP can be difficult to achieve and that an excessively high CPAP, even in spontaneous ventilation, may induce air leaks (Morley et al. 2008).

A Swiss study reported an incidence of pneumomediastinum in a neonatal and pediatric population of around 0.1 % (Hauri-Hohl et al. 2008). All neonates were at term or late preterm. Five of the nine neonates had spontaneous pneumomediastinum with no risk factors, such as mechanical respiratory support (bag mask ventilation after birth, CPAP, mechanical ventilation) or restrictive lung disease. Three of these five babies were delivered by cesarean section. In the remaining four newborns, possible mechanical incidents leading to the air leak were present. This underlines the difficulty of identifying risk factors for air leaks.

In older children, a recent paper compared the pressure characteristics of mechanical ventilation

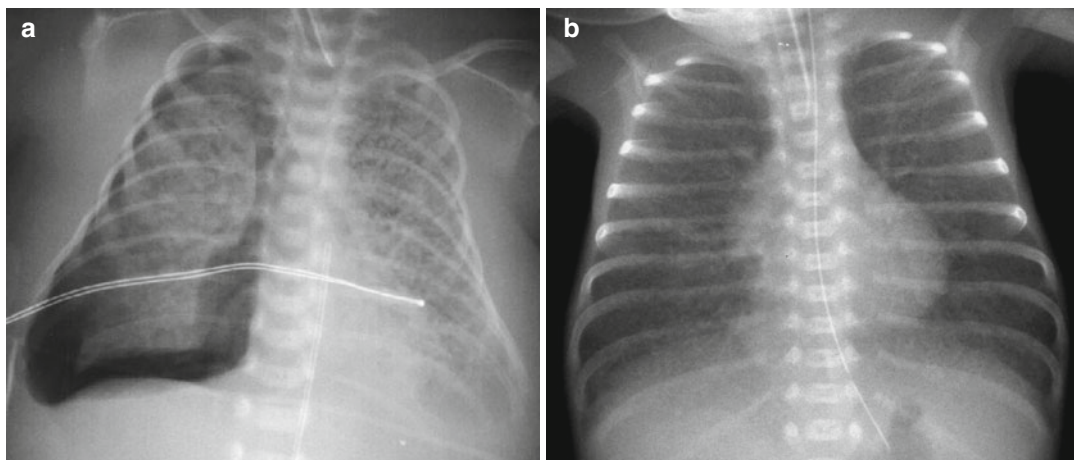


Fig. 34.1 Pulmonary interstitial emphysema. (a) Severe. This was often seen in the presurfactant era. Note the overdistension and the pneumothorax on the right side (With courtesy of Pr C. ADAMSBAUM, Pediatric

Radiology Department, Cochin-Saint-Vincent-de-Paul Hospital, Paris). (b) Mild. This is more often seen today when PIE occurs. It is limited to some linear and small cyst radiolucencies in a globally distended lung

before and after application of a lung protective strategy in two groups of comparable patients with ARDS. Thirty-three patients were studied in the first period, and 52 patients were studied in the second period: 55 % presented pneumothorax in the first period versus 17 % in the second period. The main differences in mechanical ventilation were a very high peak inspiratory pressure, PEEP, and consequently mean airway pressure. The first period was therefore marked by higher ventilatory pressures which are strongly associated with an increased rate of pneumothorax. Note that mortality was not different between the two groups in this study (Miller and Sagy 2008).

34.3 Clinical Manifestations

34.3.1 Pulmonary Interstitial Emphysema

PIE is associated with few clinical signs, but a progressive, sometimes rapid, increase in O_2 requirements and CO_2 retention are suggestive of this diagnosis. The diagnosis of PIE is therefore primarily radiographic and is frequently discovered on systematic radiographs. It is characterized, in an overinflated lung, by radiolucencies which can be linear or cystic, extending from

the pleura to the hilum (Sivit 2006), giving a “salt-and-pepper” pattern (Fig. 34.1a, b). CT scan may be helpful for the diagnosis (Jassal et al. 2008), although it is not used in routine practice.

The differential diagnosis includes lobar emphysema or, when localized, a cystic malformation of the lung (Greenough 2003). PIE must also be distinguished from air bronchogram in which branching radiolucencies follow the normal anatomic distribution of the bronchial tree.

PIE can be the cause of pneumothorax or pneumomediastinum, is frequently associated with BPD, and can be fatal with a failure to ventilate the baby.

Small subpleural blebs can be observed at autopsy but may be difficult to see post-mortem. Cystic spaces are present in the pulmonary parenchyma or in interlobular and subpleural connective tissue or in perivascular lymphatics (Greenough 2003).

34.3.2 Pneumothorax

A large pneumothorax is marked by a sudden deterioration with profound respiratory distress. Tachypnea is always present (Korones 2003). Grunting, signs of retraction with a high

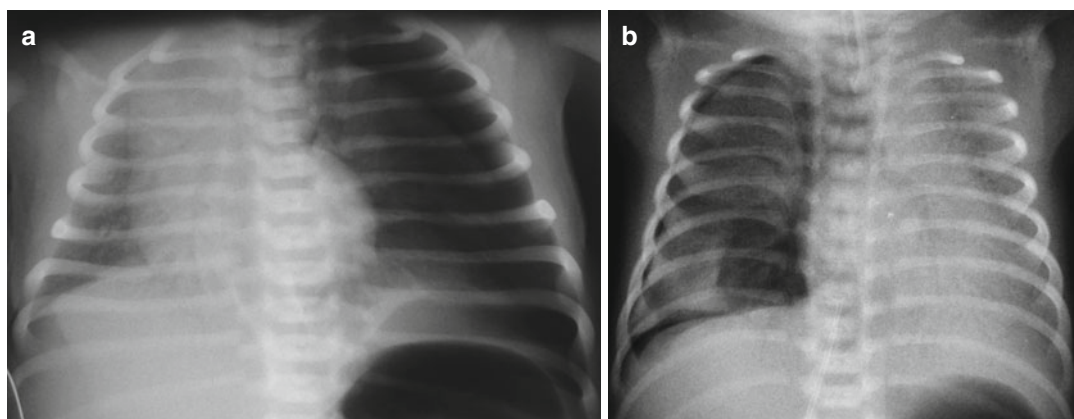


Fig. 34.2 Pneumothorax. (a) Large left pneumothorax with absence of parenchyma after the pleural line, collapsed lung, and shift of the mediastinal structures on the

opposite side. (b) Small right pneumothorax. The pleural curve is well seen

Silverman score, and cyanosis are present in all infants. On inspection, the side of the pneumothorax may be prominent compared to the other side. Abdominal distension may be observed as a result of the pressure of the pneumothorax on the diaphragm. Auscultation demonstrates decreased or absent breath sounds and a shift of heart sounds to the opposite site of the air leak. Low blood pressure and heart rate are very frequent (Ogata et al. 1976).

The diagnosis may be less obvious, also marked, in a ventilated infant, by deterioration of the respiratory status, mainly oxygenation (Ogata et al. 1976), and reduced chest wall movement. Trends in monitoring of TCPCO_2 may help to make an earlier diagnosis (McIntosh et al. 2000). Presence of risk factors such as low gestational age, RDS, and high inflation pressure as well as the presence of PIE or pneumomediastinum on radiographs should raise the suspicion of possible pneumothorax. Small pneumothoraces may be discovered only on systematic chest radiographs.

Transillumination with a fiberoptic light source is a very useful tool, especially in small infants (Kuhns et al. 1975; Watkinson and Tiron 2001), allowing a very rapid diagnosis in an infant with sudden deterioration. The light is placed on the infant's chest wall and shows increased transmission of light on the affected side which illuminates the hemithorax. It allows emergency

treatment of the pneumothorax without waiting for the radiograph.

The diagnosis is based on chest radiograph, which is mandatory in infants in a stable condition. A large pneumothorax (Fig. 34.2a) is diagnosed by the absence of lung parenchyma and a collapsed lung. If the lung is not compliant, total collapse may not be seen and signs can be limited to a small shift of mediastinal structures to the opposite side or the identification of the pleural line (Fig. 34.2b). The diaphragm may be pushed downward. Sometimes, the differential diagnosis with large pneumomediastinum may be difficult. Small pneumothoraces on radiographs taken in the supine position may also be detected only by a difference of radiolucency in one lung which appears to be "clearer" despite the presence of lung parenchyma or limited to identification of a pleural line. Two techniques can be used to confirm the diagnosis: a lateral radiograph with horizontal beam while the infant is in the supine position, which shows an anterior collection of air, and (in a stable infant) an anteroposterior radiograph with horizontal beam taken with the infant kept in lateral decubitus on the opposite side of the suspected air leak, which displays the pleural line due to the upward movement of air.

Ultrasound has also been proposed, at least for traumatic pneumothorax (Dente et al. 2007), but there are no published reports in infants.

34.3.3 Pneumomediastinum

Pneumomediastinum occurs in about 2.5 per 1,000 live births (Morrow et al. 1967). Spontaneous pneumomediastinum in healthy infants is due to the same mechanisms as spontaneous pneumothorax. Postmature infants and infants with meconium aspiration syndrome are at increased risk.

These infants, when pneumomediastinum is isolated, are usually asymptomatic or present very few signs of respiratory distress, often limited to tachypnea, a bulging sternum, and muffled heart sounds. They may sometimes be cyanosed.

The diagnosis is frequently based on systematic radiographs of ventilated infants, or when indicated by light signs of respiratory distress. Air is seen surrounding the heart on the anteroposterior view, but not extending to the diaphragmatic border (Korones 2003). Occasionally, the thymus can be seen above the heart, which is highly suggestive of pneumomediastinum. A very specific sign is the “spinnaker sail sign” (Fig. 34.3) which is due to elevation of the thymus away from the heart as a consequence of air accumulation laterally to the cardiac borders (Lawal et al. 2009). The sail is separated from surrounding structures by radiolucency. The differential diagnosis must exclude bronchogenic cyst (Shah et al. 1999).

34.3.4 Pneumopericardium

Pneumopericardium may occur in 2 % of infants hospitalized to the NICU. Hook et al. found a rate of 2 % in about 2,400 VLBW infants and 3.5 % in 1,349 ventilated infants (Hook et al. 1995).

In the majority of cases, pneumopericardium occurs in ventilated, very preterm infants with high ventilation pressures. Glenski and Hall reported 19 cases of pneumopericardium and 16 of these infants presented RDS. The striking finding was the high peak inspiratory pressure, mean airway pressure, and long inspiratory times just before the onset of pneumopericardium (Glenski and Hall 1984). Pneumopericardium can also occur in infants on nasal CPAP (Heckmann et al. 1998).

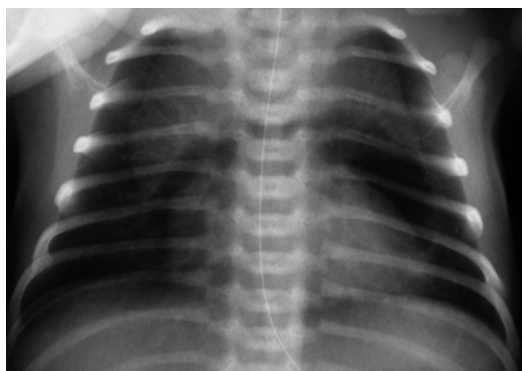


Fig. 34.3 Pneumomediastinum with the spinnaker sail sign



Fig. 34.4 Pneumopericardium. Air surrounding the heart, including the inferior part. This pneumopericardium was asymptomatic and discovered on systematic radiograph. It was treated conservatively and resolved within 24 h

Pneumopericardium may sometimes be asymptomatic and discovered incidentally on radiographs. However, it is usually responsible for cardiac tamponade with rapid deterioration including hypotension, impalpable peripheral pulses, and cyanosis. Bradycardia rapidly occurs. On auscultation, cardiac sounds are muffled or inaudible and a friction rub can rarely be heard (Greenough 2003). ECG monitoring shows a decrease of ECG voltages (Gan and Simpson 2005). The diagnosis is based on radiographs showing air surrounding the heart including the inferior surface (Fig. 34.4) and outlining the great vessels. The presence of air over the diaphragmatic surface of the heart distinguishes it

from pneumomediastinum. The transverse heart diameter may be reduced. On lateral views, air is present in the anterior part of the heart, separating it from the sternum. Pneumopericardium is responsible for a high mortality rate (Hook et al. 1995) ranging between 60 and 90 % depending on management, and may be responsible for developmental delay.

34.3.5 Pneumoperitoneum

Pneumoperitoneum is due to the same mechanisms as pneumothorax and pneumomediastinum and can therefore occur spontaneously. It is usually associated with RDS and mechanical ventilation and occurs in infants with pneumothorax or pneumomediastinum.

It is clinically asymptomatic except when a large volume of air is present, leading to abdominal distension. In massive pneumoperitoneum, the inferior vena cava may be compressed, decreasing blood return and compromising systemic circulation.

The diagnosis is radiographic, showing air in the peritoneal space (Fig. 34.5a). The lateral radiograph of the abdomen shows air collected in the superior portion of the abdomen (Fig. 34.5b) (Sivit 2006).

The main problem is to distinguish the origin of the pneumoperitoneum, as rupture of the gastrointestinal tract must be excluded. The presence of large thoracic air leaks may help to guide the diagnosis, as well as evidence of a preexisting digestive disorder. The diagnosis of an isolated intestinal perforation can be difficult. Needle aspiration of intraperitoneal air can also guide the diagnosis by showing the absence of stools or bile. Intraperitoneal gas analysis has been proposed to distinguish between pneumoperitoneum due to thoracic air leaks and bowel perforation. A partial pressure of oxygen clearly lower than that delivered by the ventilator is suggestive of surgical pneumomediastinum (e.g., of digestive origin), while a clearly higher partial pressure of oxygen is suggestive of ventilator-induced pneumoperitoneum (Vanhaesebrouck et al. 1989). A procedure using a mixture of helium

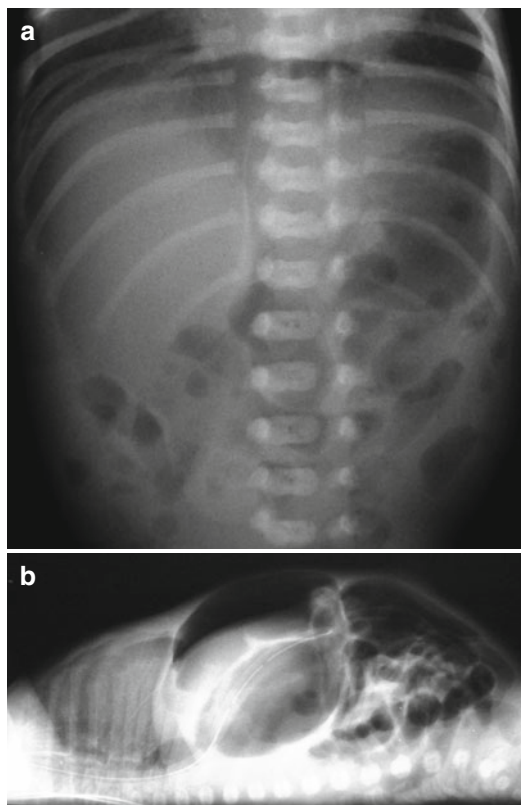


Fig. 34.5 Pneumoperitoneum. (a) Anteroposterior view showing air beneath the diaphragm, oval global translucency, and outlined falciform ligament of the liver. (b) Lateral view with horizontal beam showing air in the superior part of the abdomen and anterior to the viscera, just below the abdominal wall (Note that this pneumoperitoneum had a gastrointestinal origin)

and oxygen (heliox) has also been proposed with an analysis of intraperitoneal air showing the presence of helium (Jaarsma et al. 1999).

34.3.6 Systemic Air Embolism

Systemic air embolism is an uncommon complication (Beluffi and Perotti 2009), resulting from direct communication between the airways, connective tissue, and pulmonary vessels.

In a review of 50 cases, Lee and Tanswell showed that an air leak syndrome was present in 94 % of cases in infants with air embolism, usually presenting severe respiratory failure treated with high ventilation pressures. Clinically, the infant

presents with a sudden and dramatic deterioration with sudden collapse, pallor, cyanosis, hypotension, and electrocardiographic abnormalities. Blanching and migrating cutaneous pallor has also been reported. Air can be found in blood drawn from a catheter. There may be an unusually high oxygen tension on TcPO₂ monitoring. Radiographs may show free air in the arterial and venous systems (Lee and Tanswell 1989). The prognosis is very poor with a very high mortality. In the previous series, only 4 out of 53 infants survived.

34.3.7 Subcutaneous Emphysema

Subcutaneous emphysema is usually secondary to pneumomediastinum and is not frequently observed in neonates. Subcutaneous emphysema is easily diagnosed by the presence of subcutaneous gas which is confirmed by radiographs.

34.4 Management and Treatment Options

34.4.1 Pulmonary Interstitial Emphysema

34.4.1.1 Generalized PIE

Resolution of PIE with very short inspiratory time (Ti) has been reported (Meadow and Cheromcha 1985), but it is difficult to achieve adequate ventilation with this setting of Ti. The use of high-frequency ventilation may be a solution, at least to improve gas exchanges and to improve the radiological features of PIE, but not the long-term outcome (Keszler et al. 1991). The first studies were performed at a time when very high pressures were used for conventional ventilation (Frantz et al. 1983; Keszler et al. 1991), and it may therefore be difficult to extrapolate these results to considerably improved conditions of conventional ventilation. The use of continuous negative pressure has also been proposed (Cvetnic et al. 1989).

When PIE is very severe, precluding correct gas exchange, spontaneous or induced resolution into pneumothorax or pneumomediastinum

may help to improve ventilation. Lung puncture (Milligan et al. 1984) or placement of chest tubes in large pneumatoceles (Arias-Camison et al. 2001) may therefore constitute a possible treatment option. Surgery has been proposed but with a high mortality and appears to be a drastic procedure in a potentially reversible disease. Dexamethasone has been reported to be effective (Fitzgerald et al. 1998) but must be considered carefully in view of the current knowledge on steroids in preterm infants.

34.4.1.2 Localized PIE

The ventilatory options proposed above can also be tried in localized or unilateral PIE, but additional treatments designed to limit inflation in the affected zone can also be proposed. They are therefore dependent on the possibility to limit ventilation to the non-affected lung, but with the risk of inducing PIE in the non-affected lung.

The first option consists of placing the baby in the lateral decubitus position to promote atelectasis of the affected lung (Cohen et al. 1984) associated with cautious respiratory care including minimal chest physiotherapy and suctioning.

Selective intubation, which is easier in the right bronchus than in the left bronchus, can then be attempted with gentle ventilation to the ventilated lung, possibly using high-frequency ventilation (Randel and Mannino 1989). The non-ventilated lung becomes atelectatic and PIE resolves within 48 h (Chan and Greenough 1992). It can be difficult to selectively intubate the left main bronchus, and various intubation techniques have been proposed (Chalak et al. 2007). Ventilation of one lung can also be obtained by occlusion of a mainstem bronchus by a Swan-Ganz catheter (Rastogi et al. 2007).

Localized PIE may persist for a long time and resolve spontaneously (Jassal et al. 2008). Surgical resection can be proposed in intractable cases (Greenough 2003).

34.4.2 Pneumothorax

Pneumothorax is often asymptomatic especially spontaneous pneumothorax in otherwise healthy

infants, and does not require any treatment. Increasing the oxygen concentration has been proposed to facilitate reabsorption of extra-alveolar air (Chernick and Avery 1963) as a nitrogen washout method. To our knowledge, this widely used practice has not been evaluated in controlled trials and must be used cautiously and avoided in preterm infants due to the potential risk of oxygen.

Even in mechanically ventilated infants, the need for supplementary procedures, such as needle aspiration or drain placement, has been reviewed in a recent series (Litmanovitz and Carlo 2008). This retrospective study included 14,614 infants admitted to the NICU from 1992 to 2005, including 307 (2.1 %) infants with pneumothorax. The charts of 136 mechanically ventilated infants were reviewed (19 term, 117 preterm). Seven of the term infants were treated without a chest tube (1 with needle aspiration) and 28 preterm infants were treated without chest tube (13 with needle aspiration). This clearly indicates that a chest tube may not be necessary in ventilated infants in whom pneumothorax is well tolerated.

Needle aspiration with a syringe and a butterfly needle may be a diagnostic and emergency treatment procedure, before insertion of a chest tube, in order to obtain immediate decompression. It is usually performed with a 22–18 G butterfly needle attached to a 20–30 ml syringe via a three-way tap. The needle is inserted through the skin and then shifted slightly before going through the muscle in order to avoid air entry through the hole created after removal of the needle.

Negative pressure must be maintained in the syringe while inserting the needle into the pleura. To avoid lung puncture, it is preferable not to remove all air. Note that in the series already cited (Litmanovitz and Carlo 2008), infants treated by needle aspiration were more likely to have a chest drain than those treated by purely expectant management.

Chest drains are usually used in ventilated babies with deterioration of gas exchange or tension pneumothorax. Placement in an anterior position is essential to obtain more effective

drainage (Allen et al. 1981) but is not easily achieved via the midaxillary site (fourth to sixth intercostal spaces) usually used for insertion in order to minimize cosmetic sequelae. Chest drains inserted too deeply can also be ineffective. Two types of chest tubes can be used: the standard 10–14 Fr drain, which requires blunt dissection through the intercostal space, and a 5–6 Fr pigtail catheter (Wood and Dubik 1995) which minimizes chest wall and lung trauma due to the smaller diameter and decreased depth of insertion. Chest tubes are usually safe despite a recent report of an accident in which the catheter impaled the lung (Brooker et al. 2007). The tube is connected to an underwater sealed drain and suction is applied at a negative pressure of 10–20 cm H₂O. Heimlich valves can be used for transport. The position of the drain must be checked by radiograph, including a lateral horizontal beam chest film that shows the antero-posterior position (Fig. 34.6a, b). If drainage is insufficient, the drain position must be checked and modified if the catheter is too deep, or a second catheter can be inserted, especially when the first catheter appears to be occluded. Air bubbling in the bottle indicates that pneumothorax is still leaking. When bubbling has stopped for 12–48 h, the drain is clamped for several hours and can be removed if air does not accumulate in the pleura, e.g., if the radiograph shows no recurrence of the pneumothorax and unclamping of the drain does not result in new bubbles in the bottle. Complications of chest drains include lung perforation, chylothorax, pericardial effusion, phrenic nerve injuries, and bronchopleural fistula (Greenough 2003).

34.4.3 Pneumomediastinum

Pneumomediastinum is usually asymptomatic and therefore does not require any treatment, except a careful monitoring of the baby to detect a possible evolution towards a pneumothorax. As for pneumothorax, resorption can be accelerated by cautious administration of oxygen to term infants. Exceptionally, when pneumomediastinum induces a respiratory or circulatory dysfunction,

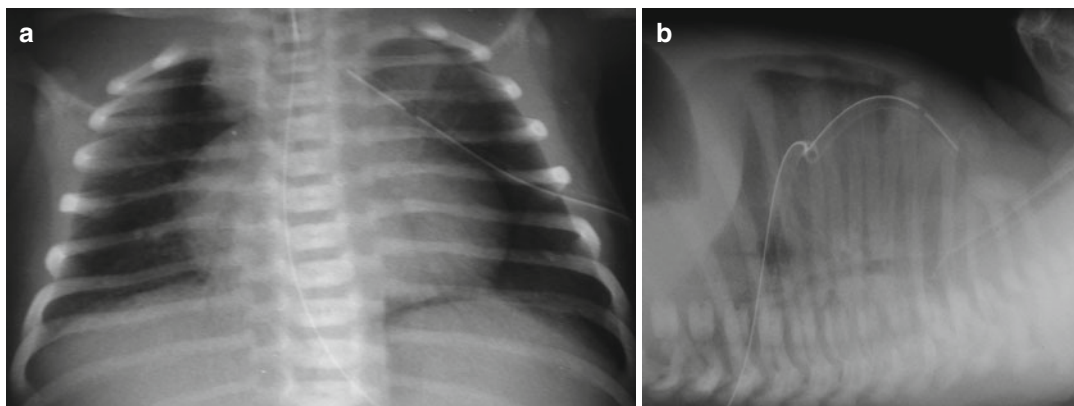


Fig. 34.6 Drained pneumothorax. (a) Anteroposterior radiograph. Note that the drain is a little too deep. (b) Lateral radiograph with horizontal beam. The drain is in anterior position and the pneumothorax is well drained

drainage may be attempted but is usually difficult. The use of high-frequency oscillation (HFO) has been proposed (Miyahara et al. 1999).

34.4.4 Pneumopericardium

When asymptomatic, a conservative approach is the best management. Oxygen has also been proposed (Hummler et al. 1996). When cardiocirculatory function is compromised, pneumopericardium must be urgently drained by needle aspiration through subxiphoid route. If this is insufficient or if pneumopericardium recurs, especially in infants ventilated with high pressures, surgical drainage can be proposed. Pneumopericardium has a poor prognosis in VLBW infants (Hook et al. 1995).

34.4.5 Pneumoperitoneum

Pneumoperitoneum usually does not need any intervention if the thoracic air leak origin has been confirmed. In the case of tension pneumoperitoneum, compromising respiratory function, needle decompression can be proposed.

34.4.6 Systemic Air Embolism

Early withdrawal of air from the umbilical arterial catheter, when present, can be useful. Infants

must be placed in the Trendelenburg position and on the left side in order to protect the brain. However, systemic air embolism is usually fatal.

34.5 Practical Measures to Reduce the Likelihood of Air Leaks in Ventilated Patients

Treatment of air leaks is mainly preventive, designed to reduce lung trauma, especially in very tiny babies with extremely stiff lungs. This can be achieved by decreasing pressures in order to obtain the minimum pressure compatible with acceptable gas exchanges. Ventilator withdrawal may be therefore the primary preventive measure, preferring a spontaneous ventilation under nasal CPAP.

However, the safety of spontaneous ventilation on continuous distending pressure must be questioned. A recent paper showed that high-flow cannulas can deliver high pressures and that a pressure-limiting valve system appears to be necessary to limit the potential for inadvertent delivery of very high distending pressures to the preterm lung (Lampland et al. 2009). A parallel observation on bubble CPAP (Kahn et al. 2007) shows that pressure must be carefully monitored.

Natural as well as synthetic surfactant is probably the most efficient way to prevent air leaks, especially when given early (Yost and Soll 2000) or as prophylaxis (Soll and Morley 2000;

Soll 2000a, b) and combined with early CPAP (Stevens et al. 2007). It is also effective to prevent air leaks as elective treatment (Seger and Soll 2009) but not when given for meconium aspiration syndrome (El Shahed et al. 2007).

Paralysis may be indicated when the infant is fighting the ventilator (Greenough 2003), but no clear result has been demonstrated on meta-analyses, possibly except for a selected population of ventilated infants with evidence of asynchronous respiratory efforts (Cools and Offringa 2005). These infants may be difficult to identify in clinical practice. The agents which can be used are discussed in another chapter.

Several ventilatory modes have been proposed to prevent air leaks with sometimes contradictory results. Moreover, some trials were performed before the widespread use of prenatal steroids and surfactant which preclude any conclusions concerning current practice.

High frequency rates in conventional ventilation has been proposed to reduce asynchrony and active expiration (Greenough et al. 1986; Greenough and Milner 1987), especially to prevent PIE (Greenough et al. 1984). High-frequency rates reduced the incidence of air leaks but in studies conducted before the age of surfactant. In order to prevent active expiration, short Ti are more efficient than long Ti to prevent air leaks (Kamlin and Davis 2004), but the five trials included in the Cochrane database meta-analysis were performed between 1980 and 1992. Even if not directly applicable to the population treated today, these studies clearly show that active expiration and asynchrony must be avoided in order to prevent air leaks.

In this view, patient-triggered ventilation has been proposed to reduce pneumothorax (Clifford et al. 1988), but the efficacy of this modality was not confirmed in randomized controlled trials and in the subsequent meta-analysis (Greenough et al. 2008). One study comparing PTV and high frequency rates in conventional ventilation even showed a tendency towards an increased incidence of pneumothorax, possibly due to the poor sensitivity of the trigger (Baumer 2000).

High-frequency ventilation raised considerable hopes for the prevention of air leaks, but meta-analyses did not show any effect of HFO on

pulmonary air leaks, or even an increased risk in various subgroups (Cools et al. 2009).

Essentials to Remember

- Air leaks can occur spontaneously in infants but are mainly linked to mechanical ventilation.
- The incidence of gross air leaks has diminished with progress in mechanical ventilation and use of surfactant.
- Prevention of gross air leaks can be achieved by finely adapting mechanical ventilation and withdrawing infants from it as soon as possible.
- Well-tolerated air leaks do not need interventions. A good monitoring of spontaneous respiration is often sufficient.

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Educational Aims

- To understand the epidemiology, risk factors, pathophysiology, and outcomes of VAP
- To have a practical approach to diagnosis and treatment of suspected VAP
- To have a practical approach to diagnosis and treatment of VAS
- To understand the modifiable risk factors for VAP and the recommended preventive measures

35.1 Ventilator-Associated Pneumonia (VAP)

Ventilator-associated pneumonia (VAP) is a common complication of mechanical ventilation in children and adults. There has been much controversy in the literature over the prevention, diagnosis, and treatment of VAP. Much of this debate is related to the fact that there is no gold standard for diagnosis of VAP, making it difficult to study without the bias introduced by different

diagnostic standards. In addition, most of the information regarding VAP comes from the adult literature, with few pediatric studies on which to base a discussion of VAP. In this chapter, this debate and some of the recent clarifications will be discussed.

35.1.1 Epidemiology of VAP

35.1.1.1 Incidence in Adult Intensive Care

In adults, VAP is the second most common nosocomial infection, accounting for 25 % of intensive care infections and 50 % of the antibiotics prescribed in intensive care. About 9–27 % of all intubated adult patients develop VAP, translating to 5–15 VAP episodes per 1,000 ventilator days. The risk for nosocomial pneumonia is 6- to 20-fold higher in ventilated adults compared to non-ventilated adults. VAP occurs at an incidence of about 3 % of ventilated patients per day during the first 5 days of ventilation, 2 % of ventilated patients per day during days 5–10 of ventilation, and about 1 % of ventilated patients per day afterwards. About half of VAP episodes are of early onset, defined as occurring in the first 4 days of ventilation (ATS 2005; Chastre and Fagon 2002).

35.1.1.2 Incidence in Pediatric Intensive Care

There are some pediatric studies examining the incidence of VAP in ventilated patients. VAP is the second most common nosocomial infection in

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Table 35.1 Incidence of VAP in children

Reference	Year	VAP criterion	n	Incidence	Per 1,000 ventilator days
Fayon et al.	1997	Consensus	439	2.5 %; 6.9 % of those ventilated ≥ 3 days	–
Richards et al.	1999	CDC criteria	110,709	2.8 %	6 (median 5, 90th percentile 12)
Raymond et al.	2000	Modified CDC	710	12.7 %	–
Fischer et al.	2000	Modified CDC	272	9.6 %	–
NNIS	2000	CDC criteria	75 PICUs	–	4.9 (median 4.6, 90th percentile 11.1)
Grobskopf et al.	2002	CDC criteria	256	6.6 %	–
Elward et al.	2002	CDC criteria	595	5.1 %	11.6
NNIS	2004	CDC criteria	52 PICUs	–	2.9 (median 2.3, 90th percentile 8.1)
Almuneef et al.	2004	Modified CDC	361	10.3 %	8.9
NHSN	2008	CDC criteria	50 PICUs	–	2.1 (median 0.7, 90th percentile 4.1)
INICC	2008	CDC criteria	1,808	7.9 %	6.1 (90th percentile 15.5)
Srinivasan et al.	2009	Consensus	58	32 %	–

CDC Centers for Disease Control of the United States, *INICC* International Nosocomial Infection Control Consortium, *NNIS* National Nosocomial Infections Surveillance, *NHSN* National Healthcare Safety Network, *PICU* pediatric intensive care unit

pediatric intensive care, accounting for over 20 % of all nosocomial infections (Richards et al. 1999). In a study from the European Multicenter Study Group, VAP was the most common nosocomial infection in pediatric intensive care (Raymond et al. 2000). As shown in Table 35.1, the incidence in various pediatric studies is 2.5–12.7 % of ventilated children, translating to 2.9–11.6 VAP episodes per 1,000 ventilator days. There have not been direct comparisons to adult intensive care patients in the same studies; however, it appears the incidence is likely slightly lower in children compared to adults. Whether this is true, and the potential reasons for this require further study.

35.1.1.3 Outcomes of VAP in Adult and Pediatric Intensive Care

Most of the data on outcomes of VAP come from the adult intensive care literature. Reviews suggest that an episode of VAP is associated with an increase in hospital length of stay of approximately 4–9 days and an increase in hospital costs of over \$15–40,000 per patient (ATS 2005; Chastre and Fagon 2002). The attributable mortality has been controversial as some studies have found no increase in attributable mortality from an episode of VAP. Nevertheless, systematic

reviews of VAP in adults suggest there is an attributable mortality in the range of 20–50 % for an episode (Safdar et al. 2005). This attributable mortality is higher in patients with associated bacteremia, VAP due to *Pseudomonas aeruginosa* or *Acinetobacter sp.*, medical patients, VAP of late onset, and for patients treated initially with ineffective antibiotics (ATS 2005; Chastre and Fagon 2002).

There is comparatively little data on outcomes of VAP in children. Fayon et al. (1997) found that multiple organ system failure “attributable” to VAP occurred in 1/12 (8 %) patients and death attributable to VAP in another 1/12 (8 %) patients. Grobskopf et al. (2002) found that those children with any pediatric intensive care unit-acquired infection, of which VAP accounted for 28 %, had a longer length of hospital stay (9.5 vs 4 days), length of intensive care stay (8 vs 2 days), and a higher age-adjusted risk of death within 4 weeks (RR 3.4, 95 % CI 1.7–6.5). Elward et al. (2002) found in a univariate analysis that children with VAP had a longer intensive care length of stay (27 vs 6 days), longer hospital length of stay (52 vs 15 days), and a higher mortality (20 % vs 7 %, $p=0.065$). Fischer et al. (2000) found that in children after cardiac surgery, VAP led

Table 35.2 Risk factors for VAP in adult intensive care units

Nonmodifiable risk factors	Potentially modifiable risk factors	
	Protective	Risk
<i>Season</i>	<i>Infection control</i>	
Fall and winter	Use of alcohol-based hand sanitizers, adequate nurse staffing	Poor practice of infection control
<i>Host factors</i>	<i>Intubation factors</i>	
Age over 60 years	Orotracheal endotracheal tube (vs nasotracheal tube), sedation protocols, ventilator weaning protocols, noninvasive ventilation	Pharmacologic paralysis, reintubation
<i>Comorbidities</i>	<i>Aspiration of microorganisms</i>	
Chronic obstructive lung disease	Semirecumbent position, post-pyloric enteral feeds, continuous aspiration of subglottic secretions, endotracheal tube cuff pressures at least 20 cm H ₂ O	Inadvertent flushing of ventilator tubing condensate down the endotracheal tube (e.g., during hospital transports, lifting of bed rails, patient repositioning)
<i>Underlying disease</i>	<i>Other factors</i>	
Acute respiratory distress syndrome, coma or impaired consciousness, burns, trauma, severity of illness, and organ dysfunctions		Stress ulcer prophylaxis with H ₂ blockers? sinusitis

to an attributable median delay of extubation of 3.7 days. Finally, Bigham et al. (2009) found that VAP was associated with PICU length of stay (19.5 vs 7.5 days), mortality (19 % vs 7 %), and ventilator days (16.3 vs 5.3 days) on univariate analysis. These studies were limited by small sample sizes, lack of multiple variable analyses, and lack of control groups; however, taken together, they do suggest that VAP in children is most likely associated with morbidity and mortality similar to the adult literature. Specifically, it is likely that an episode of VAP in children contributes to a prolonged length of stay and hospital costs and may also increase mortality.

35.1.2 Predisposing Factors for VAP

35.1.2.1 Nonmodifiable Predisposing Factors for VAP in Adult Intensive Care

Once again, most of the data for predisposing factors for VAP comes from the adult literature. It is useful to consider these risk factors for VAP in terms of modifiable and nonmodifiable risks. In the adult literature, many host and intervention factors have been identified in different studies (Table 35.2) (Chastre and Fagon 2002). Many of

these risk factors are not easily modifiable and therefore are not reasonable targets for prevention strategies for VAP (see later in this chapter).

35.1.2.2 Modifiable Predisposing Factors for VAP in Adult Intensive Care

Many studies have identified modifiable risk factors for VAP in adults. Some of the studies have obtained conflicting results, and therefore, only risk factors that have been generally accepted in the literature will be presented here. The risk factors seem to be inclusive of infection control, intubation, aspiration, colonization, and other factors (Table 35.2) (ATS 2005; Bonten et al. 2004; CDC 2004; Chastre and Fagon 2002; Collard et al. 2003; Dodek et al. 2004; Muscedere et al. 2008b).

35.1.2.3 Predisposing Factors for VAP in Pediatric Intensive Care

The applicability of the risk factors identified in adults for pediatric VAP is unclear, as there are a limited number of studies examining risk factors for VAP. Identified risk factors in the few studies include immunodeficiency, immunosuppression, and neuromuscular blockade (Fayon et al. 1997); a genetic syndrome, reintubation, and transport

out of the pediatric intensive care unit (Elward et al. 2002); female gender, postsurgical diagnosis, any narcotic use, enteral predominantly gastric feeds, and lack of any blood product administration (Srinivasan et al. 2009); enteral nasogastric feeds, prior antibiotic therapy, and bronchoscopy (Almuneef et al. 2004); and subglottic or tracheal stenosis, trauma, and tracheostomy (Bigham et al. 2009).

Some risk factors identified in adults may be difficult to extrapolate to children, such as the usefulness of noninvasive ventilation, sedation protocols, ventilator weaning protocols, continuous aspiration of subglottic secretions, and maintenance of cuff pressures at least 20 cm H₂O (which may be dangerous in smaller children due to the risk of ischemia with lower mean arterial pressures). Some risk factors in adults can likely be extrapolated to children despite the absence of good pediatric studies, including poor infection control, lower nurse staffing, poor ventilator tubing condensate management, lack of semirecumbent positioning, and lack of post-pyloric feeds. What can be said is that in children, available evidence suggests that some risk factors in adults also are true for children, including use of neuromuscular blockade, reintubation, and transports out of the pediatric intensive care unit.

Knowing the true modifiable risk factors is very important for designing practical VAP prevention strategies and studies in children. Whether some of these risk factors are indeed causative or merely associations with VAP is important. These identified risk factors need to be subjected to study to determine whether interventions to modify the risk factor prevent VAP. This question will be addressed in a later section of this chapter.

35.1.3 Pathogenesis of VAP

35.1.3.1 Colonization of the Oropharynx, Tracheobronchial Tree, and Stomach

The pathogenesis of VAP is somewhat unclear. VAP is a result of microorganisms invading the lung parenchyma. These microorganisms are

thought to be micro-aspirated into the lung prior to this invasion of the lung parenchyma.

Exactly where these aspirated microorganisms first colonize has been a matter of debate. It is known that over time, in hospitalized patients, and in particular ventilated patients, bacteria colonize the oropharynx, tracheobronchial tree, and stomach (Chastre and Fagon 2002). The sequence of colonization of these sites has been suggested to be stomach first, then oropharynx, and then tracheobronchial tree (Torres et al. 1996). However, some studies have not confirmed this, with airway colonization being preceded by oropharyngeal and not gastric colonization (Bonten et al. 1996; Cendrero et al. 1999; Ewig et al. 1999; Garrouste-Orgeas et al. 1997) or preceded by neither (Berdal et al. 2007). It is likely that the sequence of colonization is variable, and can be direct to tracheobronchial tree, or preceded by oropharyngeal and sometimes gastric colonization. Indeed, tracheobronchial colonization with potentially pathogenic bacteria occurs in ventilated patients, and when there is no lung parenchyma invasion, there is no associated VAP.

35.1.3.2 Microbiologic Epidemiology of VAP in Adult and Pediatric Intensive Care

In adults with VAP, the microbiologic organisms causing the infection are varied. In fact, VAP is often polymicrobial, in up to 50 % in some series (Chastre and Fagon 2002; Rouby et al. 1992). The organisms causing VAP are different in early-onset and late-onset VAP. Early-onset VAP is more often associated with organisms that colonize the patient's oropharynx from the community, including *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and occasionally enteric gram-negative bacilli. These organisms are said to have less resistance than the typical nosocomial bacteria that cause later-onset VAP (ATS 2005; Rotstein et al. 2008). Nevertheless, resistance in these community-acquired organisms is increasing to very high levels in some geographic regions. For example, community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) is becoming common in parts of the

Table 35.3 Etiologic organisms in VAP in children

Reference	Year	GNB (%)	<i>Pseudomonas</i> (%)	Enteric GNB (%)	GPC (%)	<i>S. aureus</i> (%)
Fayon et al.	1997	92	25	33	25	17
Richards et al.	1999	67	22	25	22	17
Raymond et al.	2000	51	36	16	26	19
Grobskopf et al.	2002	60	10	30	35	30
Elward et al.	2002	67	29	29	24	12
Almuneef et al.	2004	80	57	14	22	19
Srinivasan et al.	2009	55	3	23	50	23
Bigham et al.	2009	52	19	21	29	24

GNB gram-negative bacilli, GPC gram-positive cocci, *S. aureus* *Staphylococcus aureus*

United States and Europe, and penicillin-resistant *Streptococcus pneumoniae* is already common in many countries (Gerber et al. 2009).

Late-onset VAP, occurring at least 5 days after hospital admission, is more often associated with nosocomial bacteria that are often multiresistant to antibiotics. These organisms include *Pseudomonas aeruginosa*; *Acinetobacter* sp.; *Stenotrophomonas maltophilia*; enteric gram-negative bacilli including *Enterobacter* sp., *Klebsiella* sp., and *Citrobacter* sp.; and also MRSA (ATS 2005; Rotstein et al. 2008). Although *Candida* sp. are often isolated from secretions, this fungus is only very rarely the cause of VAP (Meersseman et al. 2009).

Although there is less data in children, the microbiology of VAP seems to be similar to that in adults. As shown in Table 35.3, there is a predominance of gram-negative bacilli including *Pseudomonas aeruginosa* and enteric gram-negative bacilli in children with VAP. *Staphylococcus aureus* and other gram-positive cocci (including *Streptococcus pneumoniae*) are also common.

35.1.4 Diagnosis of VAP

The diagnosis of VAP has been the most controversial aspect of the illness. There is little data in children. The problem has been that there is absolutely no well-accepted “gold standard” for diagnosis to use for studies of diagnostic tests. The goal of a diagnostic algorithm for VAP should be to define whether a patient has pneumonia and to determine the etiologic pathogen(s). Unfortunately, no test can reliably provide this information.

Table 35.4 Evidence-based diagnosis of VAP in studies in adult intensive care

Diagnostic technique	Sensitivity for VAP	Specificity for VAP
Clinical criteria	High	Low
Chest roentgenogram	50–78 %	Unknown. Likely <60 %
EA qualitative	High	Low
EA quantitative at 10 ⁶ CFU/ml	76 ± 9 % (range 38–82 %)	75 ± 28 % (range 72–85 %)
BAL at 10 ⁴ CFU/ml	73 ± 18 % (range 42–93 %)	82 ± 19 % (range 45–100 %)
BAL with ICO	69 ± 20 %	75 ± 28 %
PSB at 10 ³ CFU/ml	66 ± 19 % (range 33–100 %)	90 ± 15 % (range 50–100 %)
Blinded procedure (PSB or BAL)	Range 58–100 %	Range 66–100 %

EA endotracheal aspirate for culture, BAL bronchoalveolar lavage for culture, PSB protected specimen brush for culture, ICO intracellular organisms on microscopy, CFU colony-forming units

35.1.4.1 Diagnosis of VAP in Adult Intensive Care

Since VAP is associated with morbidity, mortality, and cost, a clinician needs to know the sensitivity and specificity of diagnostic tests for VAP. An evidence-based assessment of the diagnostic tests for VAP is shown in Table 35.4 (Grossman et al. 2000).

Clinical diagnosis is usually based on the presence of two or more of temperature >38 °C or <36 °C, leukopenia or leukocytosis, purulent tracheal secretions, and decreased oxygenation. A higher index of suspicion is required in the

setting of ARDS, unexplained hemodynamic instability, or deterioration of blood gases (ATS 2005; Horan et al. 2008; Chastre and Fagon 2002; Rotstein et al. 2008). If the clinical diagnosis is suspected, a chest roentgenogram (CXR) is indicated. If the CXR shows new, worsening, or persistent alveolar infiltrates or air bronchograms, then a microbiologic diagnostic test is done (ATS 2005; Rotstein et al. 2008). The microbiologic tests can include a qualitative or quantitative endotracheal tube aspirate (EA) for gram stain and culture, a bronchoalveolar lavage (BAL) for gram stain and quantitative culture, a protected specimen brush (PSB) for quantitative culture, or a blind BAL or PSB for culture (ATS 2005; Muscedere et al. 2008a; Rotstein et al. 2008). As shown in Table 35.4, each of these tests has far from perfect sensitivity and specificity (Grossman et al. 2000). The studies used to make this table had variable gold standards for VAP and often had poor documentation of antibiotic administration prior to the microbiologic test. In addition, inflammatory cells in the BAL and bacteria on gram stains of BAL have had variable sensitivity and specificity (Albert et al. 2008; Oudhuis et al. 2009; Rea-Neto et al. 2008). Blood culture also has poor sensitivity and is positive in only 8–20 % of cases of VAP (Chastre and Fagon 2002).

35.1.4.1.1 Histologic Diagnosis of VAP

By histology, VAP is often multifocal and patchy, involving both lungs, usually in the posterior and lower segments, and in different phases of evolution at different sites in the lung, often sparing peripheral lung (Chastre and Fagon 2002; Fabregas et al. 1996; Rouby et al. 1992; Torres et al. 1994, 2000). In addition, in the lungs with VAP, the microbiology is multifocal and nonhomogeneous, with different organisms not uncommon in different areas of the lung (Chastre and Fagon 2002; Fabregas et al. 1996; Pugin et al. 1991; Rouby et al. 1992; Torres et al. 1994, 2000). This suggests that culture techniques cannot be expected to have high sensitivity or specificity for VAP.

Animal data for diagnosis of VAP have the advantage of avoiding patient comorbidities, heterogeneity of underlying disease, and antibiotic

Table 35.5 Diagnosis of VAP in piglets (weight of 22 ± 2 kg) ventilated for 4 days

Gold standard for VAP	Diagnostic technique	Sensitivity for VAP (%)	Specificity for VAP (%)
Histology of the lungs	PSB	74	36
	BAL	82	33
	BAL with ICO	52	83
Lung culture at 10^4 CFU/g	PSB	35	–
	BAL	50	–
	EA	94	–

PSB protected specimen brush for culture, *BAL* bronchoalveolar lavage for culture, *ICO* intracellular organisms on microscopy, *EA* endotracheal aspirate for culture

exposure, each of which could complicate the histologic diagnosis. In a ventilated piglet model (weight 22 ± 2 kg ventilated for 4 days), histologic VAP had poor correlation with quantitative lung culture or with invasive microbiologic culture techniques (PSB and BAL), as shown in Table 35.5 (Wermert et al. 1998). Again, this suggests limitations to current invasive culture techniques for diagnosis of VAP.

There have been several postmortem studies examining the diagnosis of VAP in adults. Table 35.6 shows results of diagnostic tests compared to lung histology as the gold standard for VAP, and Table 35.7 shows results of diagnostic tests compared to lung culture as the gold standard for VAP. In general, the sensitivity and specificity of the tests are often disappointing (Rea-Neto et al. 2008).

To make matters worse, several studies show that the correlation between the actual bacteria cultured from the lung and from the invasive culture technique is not perfect. Often, only 50–80 % of the bacteria grown from the lung are also cultured from the BAL or PSB (Rea-Neto et al. 2008). In addition, only one study has examined the reproducibility of histologic diagnosis of VAP in 39 patients between four pathologists, and the prevalence of VAP diagnosed varied from 18 to 38 % (Corley et al. 1997). Finally, VAP in these studies is often present in patients not treated with antibiotics, suggesting that the diagnosis was not considered clinically (Grossman et al. 2000).

Table 35.6 Diagnosis of VAP in adults using postmortem lung histology as the gold standard

Reference	Year	Antibiotics	Diagnostic technique	Sensitivity for VAP (%)	Specificity for VAP (%)
Rouby et al.	1992	55/69 on antibiotics	NB-BAL	70	69
			NB-BAL at 10 ³ CFU/ml	45	–
Torres et al.	1994	8/30 on recent antibiotics for 3 ± 1 days	Lung biopsy 10 ³ CFU/g	40	45
			PSB 10 ³ CFU/ml	36	50
			BAL 10 ⁴ CFU/ml	50	45
			CXR with 2 clinical criteria	70	45
Marquette et al.	1995	13/28 recent antibiotics for <48 h	EA 10 ⁶ CFU/ml	55	85
			PSB 10 ³ CFU/ml	58	88
			BAL 10 ⁴ CFU/ml	47	100
			EA gram stain	50	75
			BAL with ICO	37	100
Kirtland et al.	1997	33/39 on antibiotics	Lung tissue 10 ⁴ CFU/g	11	93
			PSB 10 ³ CFU/ml	33	63
			BAL 10 ⁴ CFU/ml	11	80
			CXR with progression	55	50
Bregeon et al.	2000	1/27 recent antibiotics	Clinical judgment	100	61
			CPIS score	100	69
			Mini-BAL 10 ³ CFU/ml	50	86
Torres et al.	2000	17/25 on antibiotics for 9.5 ± 7.9 days	EA 10 ⁵ CFU/ml	35	50
			PSB 10 ³ CFU/ml	28	50
			BAL 10 ⁴ CFU/ml	37	50
			Guided lung biopsy	32	50

Inclusion criterion in the studies: Rouby: immediate postmortem pathology in those with mini-BAL done within 48 h of death. Torres: on death. Marquette: clinically suspected VAP who died within 3 days of their bronchoscopic investigation. Kirtland: on death. Bregeon: VAP suspected on death. Torres: on death

BAL bronchoalveolar lavage for culture, *EA* endotracheal tube aspirate for culture, *CXR* chest roentgenogram, *PSB* protected specimen brush for culture, *ICO* intracellular organisms on microscopy, *NB* nonbronchoscopic

35.1.4.1.2 Reproducibility of BAL and PSB to Diagnose VAP in Adult Intensive Care

In patients with at least one positive BAL (using a threshold culture of 10⁴ CFU/ml), the repeatability of two successive BAL tests was only 75 % (Gerbeaux et al. 1998). In one study of PSB (using a threshold culture of 10³ CFU/ml), for 24 % of microorganisms and 16.7 % of VAP episodes, two consecutive samples gave results spread out on each side of the threshold (Timsit et al. 1993). In another study, there were discordant results in 7.2 % overall and in 15 % of those with VAP on at least one PSB (Fox et al. 1995). In addition, the concordance between BAL and PSB for all organisms is at best <80 % (Grossman et al. 2000). In one study, the mortality rate of patients suspected to have VAP with a negative

BAL or PSB was equal to that of patients who were suspected to have VAP with positive BAL or PSB (Bregeon et al. 1997).

35.1.4.1.3 The Clinical Pulmonary Infection Score for Diagnosis of VAP

The Clinical Pulmonary Infection Score (CPIS) was initially described by Pugin et al. (1991) and is shown in Table 35.8.

In this initial study of 28 patients, the CPIS was found to correlate with the bacterial index from NB-BAL ($r=0.84$, $p<0.001$); a BI of >5 had a sensitivity of 93 % and specificity of 100 % to detect a CPIS >6 (Pugin et al. 1991). However, several subsequent reports have questioned the accuracy of the CPIS. Fartoukh et al. (2003) found that in 79 episodes of suspected VAP, a modified CPIS had a sensitivity of 82 %

Table 35.7 Diagnosis of VAP in adults using postmortem lung culture as the gold standard

Reference	Year	Antibiotics	Gold standard	Diagnostic technique	Sensitivity for VAP (%)	Specificity for VAP (%)
Chastre et al.	1995	0/20 on new antibiotics	Lung culture 10 ⁴ CFU/g	PSB 10 ³ CFU/ml	82	89
				BAL 10 ⁴ CFU/ml	91	78
				BAL with ICO	91	89
				PSB or BAL with ICO	91	89
Papazian et al.	1995	8/38 on new antibiotics	Histology and lung culture	CPIS	72	85
				PSB 10 ³ CFU/ml	42	95
				BAL 10 ⁴ CFU/ml	58	95
				BBS 10 ⁴ CFU/ml	83	80
Kirtland et al.	1997	33/39 on antibiotics	Lung culture	EA qualitative	87	31
				PSB 10 ³ CFU/ml	44	81
				BAL 10 ⁴ CFU/ml	65	63
Fabregas et al.	1999	17/25 on antibiotics for 9.5 ± 7.9 days	Histology and lung culture	CXR	92	33
				CXR with 2 clinical	69	75
				CPIS	77	42
				EA 10 ⁵ CFUL/ml	69	92
				BAL 10 ⁴ CFU/ml	77	58
				PBAL 10 ⁴ CFU/ml	39	100
				PSB 10 ³ CFU/ml	62	75
Brégeon et al.	2000	1/27 recent antibiotics	Lung culture	Mini-BAL 10 ³ CFU/ml	78	86
Torres et al.	2000	17/25 on antibiotics for 9.5 ± 7.9 days	Histology and lung culture	EA 10 ⁵ CFU/ml	62	67
				PSB 10 ³ CFU/ml	71	87
				BAL 10 ⁴ CFU/ml	71	76

Inclusion criterion in the studies: Chastre: excluded previous VAP; on death, from anterior part LLL. Papazian: on death. Kirtland: on death. Fabregas: on death. Torres: on death. Brégeon: VAP suspected on death

CFU colony-forming units, BAL bronchoalveolar lavage for culture, PSB protected specimen brush for culture, PBAL protected BAL, BBS blind bronchial sampling, CPIS clinical pulmonary infection score, ICO intracellular organisms on microscopy, EA endotracheal aspirate for culture

and specificity of 61 % for BAL-confirmed VAP. Schurink et al. (2004) reported that in 99 adults suspected of VAP, a modified CPIS had poor correlation to BAL, with a CPIS >7 having a sensitivity of 41 % and specificity of 77 % for BAL-confirmed VAP. Luyt et al. (2004) reported that for BAL-confirmed VAP, the modified CPIS >6 had sensitivity of 89 % and specificity of 47 % and CPIS >7 a sensitivity of 75 % and specificity of 66 %. Finally, Lauzier et al. (2008) reported that the receiver operating characteristic curve for the modified CPIS to diagnose late-onset VAP was not significant (meaning that no score threshold was clinically useful).

35.1.4.2 Diagnosis of VAP in Pediatric Intensive Care

There is little data in children, and most of the knowledge has been extrapolated from the above

discussion of the adult literature (Venkatachalam et al. 2011). Labenne et al. (1999) used NB-PSB and NB-protected BAL in 29 children suspected of VAP who had no change in antibiotics in the preceding 3 days. With a gold standard of clinical diagnosis (based on the CDC surveillance criteria) in 23/29 children, the results in Table 35.9 show poor sensitivity for VAP.

Gauvin et al. (2003) studied 30 children of whom 10 were diagnosed with VAP by a consensus of experts. They found the reproducibility of NB-protected BAL was moderate, with concordance for presence of bacteria 93 %, for number of bacteria 79 %, for type of bacteria 86 %, and for gram stain results 83 % (Gauvin et al. 2002). Their comparison of the different tests for VAP diagnosis is shown in Table 35.10.

Fischer et al. (1998) found the CPIS had a sensitivity of 75 % and a specificity of 70 %

Table 35.8 The clinical pulmonary infection scoring (CPIS) system

Factor	Range	Score
Temperature	36.5–38.4 °C	0
	38.5–38.9 °C	1
	>38.9 or <36.1 °C	2
Blood leukocyte count	4–11 × 10 ⁶ /L	0
	<4 or >11 × 10 ⁶ /L	1
	Above and band forms	2
	≥0.5 × 10 ⁶ /L	
Tracheal secretions	<14+	0
	≥14+	1
	≥14+ with purulent secretion	2
PaO ₂ /FiO ₂ ratio	>240 or ARDS	0
	≤240 and no evidence ARDS	2
Chest roentgenogram	No infiltrate	0
	Diffuse or patchy infiltrate	1
	Localized infiltrate	2
Culture of EA	Pathogenic bacteria ≤1+ or none	0
	Pathogenic bacteria >1+	1
	Above with same organism seen on gram stain >1+	2

A modified CPIS is sometimes used: tracheal secretions are graded as rare (0), abundant (1), and abundant and purulent (2); and microbiology of EA is graded as negative (0) or positive (2)

Table 35.9 Invasive diagnosis of VAP in a study in children

Diagnostic technique	Sensitivity for VAP (%)	Specificity for VAP (%)
EA qualitative	93	41
PSB 10 ³ CFU/ml	69	95
BAL with ICO (≥1 %)	55	89
BAL 10 ⁴ CFU/ml	72	88

Gold standard for VAP was a clinical diagnosis based on the CDC criteria

EA endotracheal aspirate for culture, PSB protected specimen brush for culture, BAL bronchoalveolar lavage for culture, ICO intracellular organisms on microscopy

compared to a gold standard of VAP diagnosed retrospectively by two experts.

In summary, the limited results of pediatric studies are compatible with the results summarized for the large literature in adult intensive care.

Table 35.10 Invasive diagnosis of VAP in a recent study in children

Diagnostic technique	Sensitivity for VAP (%)	Specificity for VAP (%)
CDC criteria	100	15
B-PBAL 10 ⁴ CFU/ml	50	80
B-PBAL 10 ³ CFU/ml	60	75
B-PBAL with ICO	30	95
B-PBAL gram stain organisms	50	81
B-PBAL with BI >5	78	86
EA qualitative	90	40

Gold standard for VAP was consensus of 2/3 experts given the hospital chart data for the 2 days before BAL, the day of BAL, and the following day

B-PBAL blind protected bronchoalveolar lavage for culture, ICO intracellular organisms on microscopy, BI bacterial index, EA endotracheal tube aspirate for culture

35.1.5 Treatment of VAP

The lack of a true gold standard for diagnosis of VAP has complicated the interpretation of the literature of treatment of VAP. Given the limitation of the literature on diagnosis of VAP discussed above, the focus must be on outcomes research: what is the outcome of using a particular strategy for diagnosis and treatment of VAP over another strategy? Since there is virtually no data in children, all of this discussion is extrapolated from adult data.

35.1.5.1 General Considerations for Treating VAP

There are several general points to be made in treatment of VAP (Table 35.11).

First, there should be no delays in initiating antibiotic treatment of clinically suspected VAP (ATS 2005; Muscedere et al. 2008a; Rotstein et al. 2008). Delay of >24 h in starting appropriate antibiotics is an independent risk factor for hospital mortality in logistic regression analyses (adjust OR 7.68, 95 % CI 4.5–13.09) (Iregui et al. 2002).

Second, broad-spectrum antibiotics should be started empirically in order to avoid inappropriate antibiotic coverage. Multiple studies have shown that initially inappropriate antibiotics for VAP are associated with significant increases in mortality (ATS 2005; Chastre and Fagon 2002).

Table 35.11 General priorities in management of VAP in children or adults

General principle	Details
Initiate antibiotic treatment urgently	Delays of antibiotic treatment are associated with mortality
Empiric treatment should be broad spectrum enough to cover all likely pathogens	Inappropriate initial antibiotics are associated with mortality
Duration of antibiotics can be ≤ 8 days	Shorter course of therapy (than the traditional 14 days) in clinically responding patients does not change outcome and reduces antibiotic resistance
De-escalation of antibiotics is often appropriate on days 2–3 after assessing culture results and clinical response	Some observational studies suggest this is safe, and it should reduce antibiotic resistance in intensive care
Known risk factors for multidrug-resistant bacteria causing a VAP	Risk factors require initial antibiotics to be broader spectrum to cover these organisms prevalent in the particular hospital and community
The microbiologic diagnosis technique does not change outcome	An EA, BAL, and PSB, blind or bronchoscopic, are all likely equivalent for helping guide management
Consider the clinical course of the patient on therapy	Most findings should be resolving within the first 6 days of treatment. If they are not, consider other sites of infection, other reasons for lung infiltrates, and resistant bacteria

EA endotracheal aspirate, BAL bronchoalveolar lavage, PSB protected specimen brush

This may be the most important independent determinant of hospital mortality (adjusted OR 4.27, 95 % CI 3.35–5.44) (Kollef et al. 1999). This is also true in those patients with a less severe degree of illness: in one study, the odds ratio for hospital mortality was 0.22 if adequate antibiotics were started on day 0 (the day of suspicion of VAP) in those patients with low severity of illness scores (Clec’h et al. 2004). Somewhat surprisingly, some studies have suggested that changing therapy based on culture results to treat an initially inadequately treated organism does

not reduce mortality (Clec’h et al. 2004; Luna et al. 1997).

Thirdly, the duration of antibiotics given to treat VAP can be shorter than traditionally used. Chastre et al. (2003) conducted a randomized controlled trial of 8 days versus 15 days of antibiotic therapy for VAP in adults, with no significant differences in outcomes in the two groups (including death on day 28, day 60, and in the hospital and lung infection recurrence). Micek et al. (2004) conducted a randomized controlled trial of an antibiotic discontinuation policy for clinically suspected VAP, with discontinuation based on resolution of symptoms and signs of VAP. Antibiotics were given for 6 ± 4.9 days versus 8 ± 5.6 days in the two groups. No significant differences in secondary episodes of VAP, hospital mortality, or intensive care length of stay were found between the groups. Singh et al. (2000) conducted a randomized trial of short-course empiric antibiotic therapy versus conventional treatment for patients with pulmonary infiltrates in the intensive care unit. Those randomized to 3 days of ciprofloxacin for a CPIS < 7 on day 0 and again on day 3 had less antibiotic resistance, and a trend to lower mortality, without a change in length of stay.

Fourth, de-escalation of antibiotic therapy is encouraged after culture results and clinical course are known. This is based on the overuse of broad-spectrum antibiotics that results in increasing antibiotic resistance in intensive care units (ATS 2005; Goffken and Niederman 2002; Leone et al. 2007; Kollef et al. 2006; Torres et al. 2009). However, the utility of this approach has not yet been rigorously studied. Some observational studies suggest that de-escalation based on improving clinical course and culture results is safe (Joffe et al. 2008; Shorr et al. 2005).

Fifth, one must keep in mind risk factors for resistant bacteria. Resistant bacteria are more common in patients with a longer hospital length of stay, longer duration of ventilation, and prior antibiotic administration (Rotstein et al. 2008). The American Thoracic Society suggests considering nosocomial bacteria in patients with antimicrobial therapy in the preceding 90 days, current hospitalization of 5 days or more, a high

frequency of antibiotic resistance in the community or the specific hospital unit, immunosuppressive disease or therapy, or another risk factor including hospitalization for 2 days or more in the preceding 90 days, home infusion therapy, residence in an extended care facility, chronic dialysis within 30 days, home wound care, or a family member with a multidrug-resistant pathogen (ATS 2005). In children, chronic neurological disability seems to be a risk factor for more resistant bacterial flora.

Sixth, the microbiologic technique used does not likely change clinically significant outcomes. There have been several outcome studies of an invasive approach (bronchoscopy) to diagnose VAP. In a meta-analysis of four trials ($n=628$ patients), the invasive versus noninvasive (EA) diagnostic strategy was not associated with any change in mortality, though there were more changes in antibiotic management in the bronchoscopic strategy (Shorr et al. 2005). A more recent randomized controlled trial found no differences in any outcome comparing a bronchoscopic versus a noninvasive (EA) strategy for microbiologic diagnosis of VAP (CCCTG 2006).

Finally, one must consider the clinical course of the patient during treatment. Dennessen et al. (2001) found significant improvement in all clinical parameters within the first 6 days after start of antibiotics. The mean (median) days to resolution of parameters were fever 5 (3) days, $\text{PaO}_2/\text{FiO}_2$ ratio 6 (2) days, leukocyte count 8 (6) days, and number of bacteria CFU/ml in EA 10 (7) days. Enterobacteriaceae, *S. aureus*, and *P. aeruginosa* persisted in EA despite antibiotics and clinical response. Newly acquired colonization with Enterobacteriaceae and *P. aeruginosa* occurred during the second week. Similarly, Luna et al. (2003) found improved secretions and temperature during the first 3–7 days of treatment and variable response of leukocyte count over time. In survivors with VAP, the $\text{PaO}_2/\text{FiO}_2$ ratio resolved more quickly (by days 3–5). The American Thoracic Society suggests that initial CXR deterioration is common, and improvement of the CXR often lags behind clinical resolution. However, progression to multilobar involvement, a >50 % increase in size of infiltrate, or

significant pleural effusion should raise concern of nonresponse to therapy (ATS 2005). If the clinical course fits the above resolution process, this suggests that a short course of treatment is adequate, and de-escalation of antibiotics can be considered. If the clinical course does not fit, one should question the diagnosis (i.e., is there another cause of lung infiltrates, or for fever) and the antibiotic therapy being used (ATS 2005).

35.1.5.2 Antibiotic Considerations for Treating VAP

There are a number of considerations in choosing antibiotics to treat VAP.

First, the antibiotics should cover the likely pathogens that cause VAP at the particular institution. The microbiology is often polymicrobial and can include resistant flora (ATS 2005; Rotstein et al. 2008).

Second, early-onset VAP in the first 4 days of hospital admission, and without risk factors for resistant flora mentioned in the above section of this chapter, is usually associated with less resistant microbes. The American Thoracic Society recommends initial treatment with ceftriaxone, ampicillin/sulbactam, or ertapenem (ATS 2005). Cefotaxime, cefuroxime, and, in severe early-onset VAP, piperacillin/tazobactam may also be considered (Fowler et al. 2003). If MRSA is a consideration, then linezolid should be added (Wunderink et al. 2003). Whether vancomycin is a suitable alternative for MRSA pneumonia is controversial, with some retrospective data suggesting a poor clinical response (Wunderink et al. 2003; Luna et al. 2009).

Third, for late-onset VAP (day 5 or later of hospital admission), or in VAP with risk factors for resistant flora, antibiotics treating organisms of concern in the institution, such as *P. aeruginosa*, extended-spectrum beta-lactamase producing *Klebsiella sp.* or *E. coli*, and *Acinetobacter sp.*, should be used. Potential antibiotics include antipseudomonal cephalosporins (cefepime, ceftazidime), antipseudomonal carbapenems (imipenem, meropenem), and a beta-lactam with beta-lactamase inhibitor (piperacillin/tazobactam) with or without an antipseudomonal fluoroquinolone (ciprofloxacin) or aminoglycoside (gentamicin,

tobramycin, or amikacin). One should also consider MRSA if prevalent at the institution and add linezolid or potentially vancomycin to the regimen (ATS 2005; Rotstein et al. 2008).

Fourth, whether mono- or dual-antibiotic coverage is required is controversial. In a recent randomized trial of combination (meropenem and ciprofloxacin) versus monotherapy (meropenem) for empiric treatment of suspected VAP, there was no difference in 28-day mortality, duration of intensive care or hospital stay, clinical or microbiologic treatment response, emergence of antibiotic-resistant bacteria, or *Clostridium difficile* infection (Heyland et al. 2008). This suggests that monotherapy with a broad-spectrum antipseudomonal antibiotic may be an adequate empiric treatment. Recent meta-analysis of beta-lactam and aminoglycoside antibiotics for patients with sepsis, cancer, or neutropenia, with gram-negative bloodstream infections, and *Pseudomonas* infections has found that combination therapy is not superior to monotherapy for clinical outcomes or emergence of resistance (Paul et al. 2003, 2004). Whether this monotherapy strategy applies to centers with high resistance rates is unknown, given the data that inadequate initial antibiotics in VAP are associated with mortality. If dual therapy is used, it is not for “double coverage,” but rather it is to ensure that single coverage of all potential pathogens is present in the empiric regimen. Based on culture results and clinical course, de-escalation to monotherapy in these patients seems reasonable (Joffe et al. 2008).

35.1.5.3 Strategies for Diagnosis and Treatment of VAP in Adult Intensive Care

Several strategies for VAP management have been published. The American Thoracic Society suggests that on VAP clinical suspicion, a lower respiratory tract sample for culture and microscopy be obtained, by any method (EA, BAL, or PSB). Empiric antimicrobial therapy should then be started unless there is a very low clinical suspicion for VAP and negative microscopy of the lower respiratory tract sample. The patient should be reassessed on days 2–3 to determine their culture results and clinical response (temperature,

leukocyte count, CXR, oxygenation, sputum, hemodynamic changes, and organ dysfunctions). If there has been clinical improvement at 48–72 h, then de-escalation of antibiotics based on culture results (including stopping antibiotics if cultures were negative) is suggested, with a duration of treatment of 8 days. If there is no clinical improvement, then other sites of infection, complications, and diagnoses must be considered (ATS 2005).

The Surviving Sepsis Campaign suggests either a quantitative or clinical strategy to treatment. The quantitative strategy (using immediate sampling of distal airways and direct stain of BAL or PSB) suggests immediate antibiotics in those patients with bacteria present on stain or with severe sepsis. The clinical strategy (using immediate EA) suggests immediate antibiotics and de-escalation based on culture results (Cohen et al. 2004).

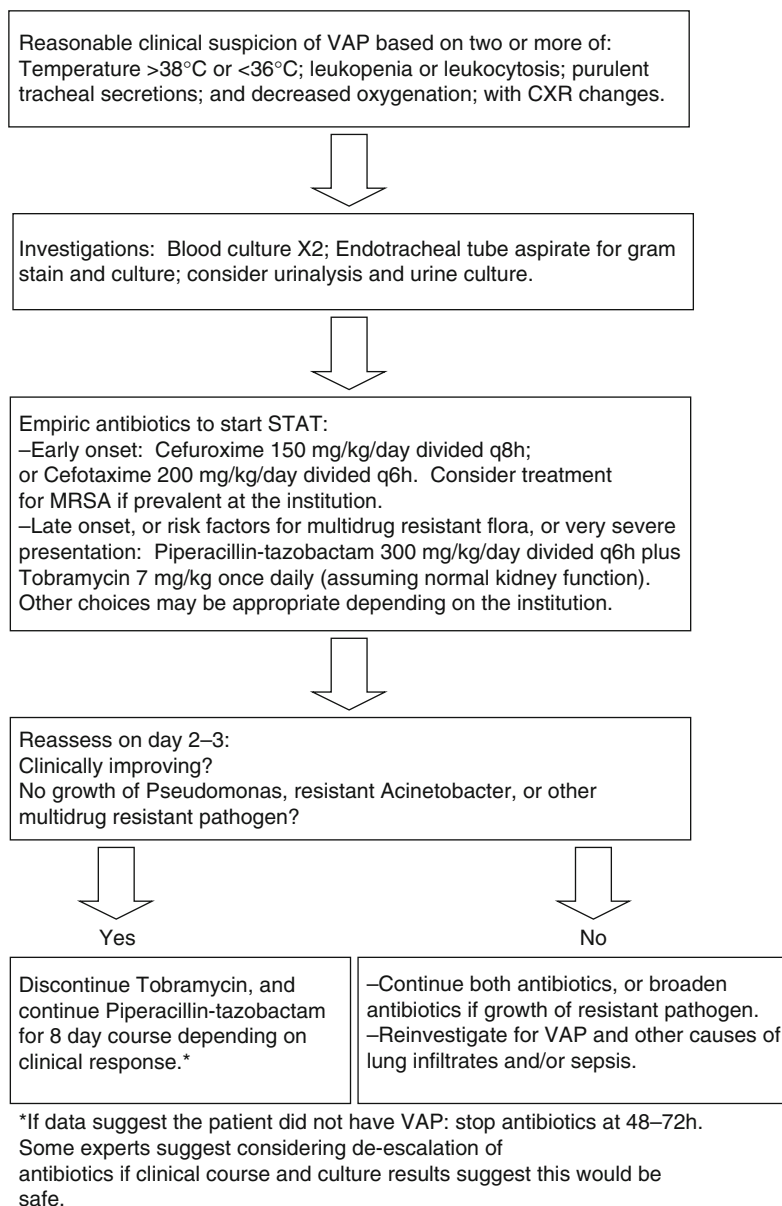
A recent Canadian evidence-based clinical practice guideline for VAP suggests EA with non-quantitative cultures be used as the initial diagnostic strategy for VAP, empiric therapy when VAP is clinically suspected, and appropriate spectrum monotherapy for empiric therapy. The duration of antibiotics in those who receive adequate initial treatment is a maximum of 8 days, and an antibiotic discontinuation strategy is suggested. The choice of empiric antibiotic should be based on local resistance patterns and patient factors (Muscedere et al. 2008a).

The Association of Medical Microbiology and Infectious Disease Canada and the Canadian Thoracic Society have also published guidelines recently. The main difference from the above guidelines is that the CPIS is emphasized: if it is 6 or less, and on day 3 remains 6 or less, then therapy is stopped on day 3, based on the study by Singh et al. (2000). If the CPIS is <4, then antibiotic therapy is not recommended (Rotstein et al. 2008).

35.1.5.4 A Suggested Strategy for Diagnosis and Treatment of VAP in Children

There are no outcome studies of different strategies for managing VAP in children. Based on the adult data reviewed above, an approach is suggested in Fig. 35.1.

Fig. 35.1 An approach used to diagnosis and treatment of VAP used at the authors' institution



35.1.6 Prevention of VAP

There have been many studies of prevention in adult intensive care, but none in children. Recent systematic reviews and meta-analyses have determined which strategies are most useful (Table 35.12) (ATS 2005; Bonten et al. 2004; CDC 2004; Chastre and Fagon 2002; Collard et al. 2003; Dodek et al. 2004; Muscedere et al. 2008b; Rotstein et al. 2008).

The most important strategies for prevention are infection control measures including alcohol-based hand disinfection, and condensate in the ventilator tubing should be prevented from entering the endotracheal tube (especially on repositioning the patient and transport). Raising the head of the bed 45° was effective in one randomized trial (Drakulovic et al. 1999), but was not confirmed in another trial where the head of bed was usually only raised to 30°

Table 35.12 Prevention strategies for VAP in intensive care units

Strategy	ATS (2005)	Collard et al. (2003)	Dodek et al. (2004)	Bonten et al. (2004)	CDC (2003)	Muscedere et al. (2008b)	Rotstein et al. (2008)
<i>General strategies</i>							
Infection control: education, alcohol hand disinfection, surveillance, and feedback	+	–	–	+	+	–	+
Adequate nurse staffing	+	–	–	+	–	–	–
<i>Ventilation strategies</i>							
Avoid reintubation	+	–	–	+	+	–	–
Use noninvasive ventilation when indicated	+	–	–	–	+	–	–
Use orotracheal intubation route	±	–	+	+	+	+	+
Use aspiration of subglottic secretions to reduce early-onset VAP	+	±	±	+	+	+	+
Keep endotracheal tube cuff pressure at least 20 cm H ₂ O	+	–	–	+	–	–	+
<i>Aspiration prevention strategies</i>							
Use semirecumbent position	+	+	+	+	+	+	+
Use enteral rather than parenteral nutrition	+	–	–	–	–	–	–
Use post-pyloric enteral feeds	+	–	–	+	–	–	–
Avoid paralytic agents	+	–	–	–	–	–	–
Avoid inadvertently emptying condensate in ventilator tubing into airway	+	–	–	+	+	–	+
<i>Other strategies</i>							
Stress ulcer prophylaxis without H ₂ blockers	–	+	–	+	–	–	–
Oral antiseptics	±	–	–	+	±	±	±
Kinetic beds	–	±	±	–	–	±	±
Selective digestive tract decontamination	–	–	–	+	–	–	–
Decreased frequency of ventilator circuit changes	+	+	+	+	+	+	+
Heat and moisture exchanger versus heated humidifier	–	±	+	±	–	–	±

+ recommend this strategy; – no recommendation or recommendation against; ± recommend considering this strategy in some circumstances

(van Nieuwenhoven et al. 2006). There should be no routine replacement of ventilator tubing unless it is visibly soiled (Dodek et al. 2004).

Reintubation is to be avoided if possible; however, it is unclear how realistic this suggestion is (ATS 2005; CDC 2004).

The issue of antibiotic prophylaxis is a difficult one. In general, reviews of selective digestive decontamination (SDD) show that it is effective in preventing VAP, but has inconsistent effect on mortality, length of stay, and length of mechanical ventilation (Bonten et al. 2004). Based on concern for development of resistant flora, and the lack of consistent mortality benefit, SDD has not been widely implemented, particularly in North America (ATS 2005; Muscedere et al. 2008b; Rotstein et al. 2008; Torres et al. 2009). Selective oral decontamination (SOD) is another potential strategy. A recent meta-analysis found oral application of antibiotics did not significantly reduce the incidence of VAP; but, oral application of antiseptics significantly reduced the incidence of VAP. However, neither strategy reduced mortality, duration of mechanical ventilation, or stay in the intensive care unit (Chan et al. 2007). This debate is ongoing, with a recent large randomized trial of 5,939 adult intensive care patients in the Netherlands showing on an adjusted analysis that SDD and SOD had OR for death at 28 days of 0.83 (95 % CI 0.72–0.97) and 0.86 (95 % CI 0.74–0.99), respectively (de Smet et al. 2009). Whether the use of prophylactic topical oropharyngeal antiseptics is implemented widely remains to be seen.

Implementing prevention strategies into “bundles” has been advanced by various collaborative groups that are working to reduce nosocomial infections. These strategies can be implemented onto a checklist at the bedside that is reviewed at least daily. With local champions to advocate the importance of prevention of this serious infection, the intensive care team can take ownership of their VAP prevention packages. At one center, a bundle including the following strategies was implemented: good handwashing with soap and water or alcohol-based hand rinse between patients and between contaminated sites on the same patient, head of bed elevation with ventilator tubing falling away from the patient to ensure condensate is not instilled to the patient, and keeping the Yankauer used to suction mouth covered and rinsed between uses. With this, there was a significant decrease in VAP rates (Bigam et al. 2009).

35.2 Sinus Infections in the Intensive Care Unit

Ventilator-associated sinusitis (VAS) has been a problematic entity in the literature. It has remained somewhat unclear how common VAS is and how aggressively to search for and treat VAS. There are no pediatric studies regarding VAS.

35.2.1 Epidemiology of VAS

In adult intensive care, VAS is not uncommon. By computed tomographic scan in ventilated patients, 30–50 % have sinus opacification or air-fluid levels (Westergren et al. 1998). In prospective investigations by antral puncture and culture, about 15–30 % of patients ventilated by nasotracheal tube for more than 5–7 days have VAS (Westergren et al. 1998). The risk factors for VAS have not been well investigated; however, it seems that the risk is significantly higher in those ventilated with a nasotracheal tube. In some observational investigations, the incidence of VAS in those ventilated by orotracheal tube is 2–6 % as opposed to 42 % when ventilated by nasotracheal tube (Westergren et al. 1998). However, one randomized trial found no statistically significant difference in the incidence of VAS in those ventilated for >7 days and randomized to orotracheal tube and orogastric tube versus those randomized to nasotracheal tube and nasogastric tube (Holzapfel et al. 1993). Other risk factors may include maxillofacial trauma, and nasogastric tubes, although confirmation of these has been lacking (Westergren et al. 1998).

The microbiology of VAS is similar to that of VAP. In a review of the literature, it was found that gram-positive cocci (predominantly *Staphylococcus aureus* and Streptococcaceae) were found in 32 %, gram-negative bacilli (predominantly *Pseudomonas aeruginosa*, *Acinetobacter* sp., enteric gram-negative bacilli, and *Haemophilus influenzae*) in 54 %, anaerobes in 4 %, *Candida* sp. in 9 %, and polymicrobial in over half of cases (Westergren et al. 1998).

The outcomes of VAS are unclear. There is one randomized study assessing the systematic

search for maxillary sinusitis in the nasotracheally ventilated adult patient. In 399 patients randomized to serial routine CT scans for fever ($n=199$) versus standard care ($n=200$), it was found that radiographic and microbiologic sinusitis occurred in 55 and 39 % of the study group versus none of the standard care group patients. VAS increased the risk of VAP by 1.60 (95 % CI 0.8–3.56; $p=0.17$). Two-month overall mortality was 36 % in the study group versus 46 % in the control group ($p=0.03$), and antibiotics were given more often in the study group (Hozapfel et al. 1999). In studies of VAS, the same organisms are cultured from the sinus and the VAP in 38–56 % of patients (Hozapfel et al. 1999; Westergren et al. 1998). Some studies have documented the same organism cultured from VAS and the blood in 12–37 % of patients with VAS (Hozapfel et al. 1999). These results are difficult to interpret for the following reasons: the effect of VAS on mortality requires confirmatory studies; and sinuses and airways can be colonized with the same microbial floras that are at other sites, and therefore, culturing the same organisms does not prove VAS was the source.

35.2.2 Diagnosis and Treatment of VAS

As in VAP, the diagnosis of VAS is confounded by the poor specificity of radiologic investigation and the ease of contamination of sinus samples for microbiologic culture. Signs of sinusitis such as headache and facial pain may be impossible to elicit, and purulent nasal discharge may be insensitive and nonspecific for sinusitis (Cohen et al. 2004; Marshall et al. 2004; O'Grady et al. 2008; Rizolli and Marshall 2001; Westergren et al. 1998). Roentgenograms of the sinuses are nonspecific and technically not feasible in the intensive care unit. Computed tomography of the sinuses requires patient transport, and also is nonspecific, as opacities and air-fluid levels in maxillary sinuses are

culture positive approximately half of the time (Westergren et al. 1998). Even then, it is difficult to sterilize the route of access to the sinus cavity for cultures and therefore difficult to discern colonization from infection in the sinuses (Westergren et al. 1998). Puncture and aspiration of the involved sinuses under aseptic conditions for culture for aerobic, anaerobic, and fungal organisms is recommended to diagnose VAS (Cohen et al. 2004; Marshall et al. 2004; O'Grady et al. 2008). The maxillary sinus is usually entered through the canine fossa after antiseptic is applied to the gingiva. One study found that the contamination rate was 67 % using this technique and recommended a free bone area made in the canine fossa, avoiding contact with the oral mucosa, and with a contamination rate of 5 % (Westergren et al. 1998). How feasible and safe these techniques are in children is not clear, and there has not been study of their safety and yield in pediatric intensive care. Sinoscopy can suggest an inflammatory state in the sinus cavity, but how sensitive and specific the appearance is for infection is not known (Westergren et al. 1998).

Given these problems, diagnosis of VAS is difficult and often nonspecific. In a patient with fever and no known focus of infection, it may be reasonable to image the sinuses with computed tomography. If there is opacification or air-fluid level in maxillary sinus, it also may be reasonable to have an ear-nose-throat specialist aseptically aspirate the involved sinus for cultures. If fungal infection is suspected, a sinus mucosa biopsy may also be useful. The sinus aspirate may be therapeutic and diagnostic. If bacteria are present on gram stain or culture, then antibiotic treatment would be reasonable (Cohen et al. 2004; O'Grady et al. 2008; Marshall et al. 2004). The duration of therapy required is unknown, but it would likely be reasonable to treat similarly to VAP. Some recommend also changing any nasal tubes to oral ones, including orogastric and orotracheal, although the usefulness of this to facilitate drainage and resolution is unstudied.

Essentials to Remember

Summary of VAP in Pediatric Intensive Care

There have been many controversies in the VAP literature, often due to the fact that there is no gold standard for the diagnosis of VAP. VAP is common and associated with significant adverse outcomes including length of stay, hospital costs, and mortality. The diagnostic and treatment strategy needs to be studied using an outcomes research design: the effect of different strategies on outcomes of mortality, ventilator days, length of stay, antibiotic resistance, and hospital costs. The adult intensive care literature has made significant advances in this regard, while the pediatric literature is very limited. Priorities in management have been outlined here, including clinical suspicion of VAP, noninvasive microbiologic testing, immediate empiric antibiotics to cover all likely potential pathogens, and, after reassessment on days 2–3 of treatment, consideration of de-escalation of antibiotic therapy.

Summary of VAS in Pediatric Intensive Care

VAS is an unstudied disease in pediatric intensive care. In adults, radiologic sinus disease is not uncommon, but is nonspecific for infection. In an adult patient with fever of unknown source, it is reasonable to perform computed tomography, and if opacification or air-fluid level in the maxillary sinus is seen, aseptic aspiration of the sinus cavity via the canine fossa for gram stain and culture is recommended to diagnose VAS. The safety and usefulness of this invasive approach in children is unstudied. If VAS is confirmed, antibiotic treatment is reasonable. The outcomes associated with VAS are unclear. In addition, the usefulness of removal of nasal tubes to facilitate treatment of VAS is unstudied.

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36.1 Introduction

While endotracheal intubation is often necessary to facilitate mechanical ventilation for critically ill children, it has been associated with the development of upper airway obstruction upon extubation (Koka et al. 1977; Stoelting and Procter 1968; Pender 1954). With the evolution of intubation, sedation, and mechanical ventilation practices in pediatric intensive care units, the overall incidence of severe post-extubation stridor has decreased, and long-term complications from endotracheal intubation such as subglottic stenosis (Strong and Passy 1977; Markham et al. 1967; Abbott 1968) are now infrequent. Nonetheless, post-extubation stridor results in short-term morbidity with increased length of mechanical ventilation and intensive care unit (ICU) length of stay (Kurachek et al. 2003).

Post-extubation stridor is common in PICUs, with incidence rates that range from 6 to 30 %

(Tellez et al. 1991; Deakers et al. 1994; Newth et al. 2004) and may be as high as 69 % (Anene et al. 1996) in high-risk groups. Moreover, post-extubation stridor results in reintubation 2–6 % (Tellez et al. 1991; Deakers et al. 1994; Newth et al. 2004) of the time or up to 22 % in high-risk groups (Anene et al. 1996).

Unfortunately, characterizing upper airway obstruction after extubation is not standardized, and there is often disagreement among practitioners as to what degree upper airway obstruction contributes to the need for reintubation. In fact, based on clinical grounds alone it is estimated that up to 1/3 of all failed extubations are a consequence of upper airway obstruction (Kurachek et al. 2003; Edmunds et al. 2001), although these observations have not been confirmed with objective measures of airway obstruction (Argent et al. 2008a). As such, the subjective nature of this assessment likely contributes to the variability in reported incidence and may explain the inconsistent response to potential therapies such as corticosteroids, racemic epinephrine, or heliox.

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Educational Goals

- Review the pathophysiology of post-extubation airway obstruction, the epidemiology, known risk factors for its development, clinical and physiologic measures of severity of upper airway obstruction, and finally treatment or prevention options.

36.2 Anatomical Considerations of the Pediatric Airway

The infant and child are particularly prone to upper airway obstruction for several reasons. Anatomically, the configuration of the airway changes considerably as a child develops from infancy to adulthood. The infant's airway is characterized by a relatively small mouth because of a small mandible and flat roof of the nasopharynx (Fujioka et al. 1979; Arens et al. 2002; Wheeler et al. 1998). As the child develops, the mandible descends and moves forward, and the roof of the pharynx becomes more rounded. Moreover, the tongue is relatively large compared to the bony structures in the mouth, and the normal anterior displacement of the tongue with inspiration is relatively blunted in the young infant. As a result, loss of airway tone from sedation, sleep, or CNS dysfunction is more likely to result in obstruction of the posterior pharynx in a young child, than in an adult (Isono et al. 2000).

Descending down the airway into the larynx, compared to an adult, an infant's larynx is high in the neck and at birth the epiglottis often overlaps the soft palate, at the level of the first cervical vertebrae. The epiglottis separates from the soft palate by approximately 6 months of age and descends to the third cervical vertebrae. It reaches the adult position, at the fifth or sixth cervical vertebrae, by adolescence. The infant's epiglottis is rounder and softer than the adult epiglottis and is more prone to occlude the airway. Finally, the larynx of an infant tapers in a funnel shape and becomes narrowest at the cricoid cartilage, in the subglottic space. It remains this way until about 8–10 years of age, when, like adults, the narrowest portion is at the level of the vocal cords (Arens et al. 2002).

The resistance of a tube (such as the trachea) is inversely proportional to the radius raised to the fourth power under laminar conditions or to the fifth power under turbulent flow. A small change in airway caliber can result in significant increases in airway resistance. This is of course exaggerated in small children, where a small amount of circumferential airway edema can result in a relatively larger increase in airway

resistance than a similar amount of edema in an adult or large child.

Because of this predisposition to upper airway obstruction, post-extubation stridor has historically been a more common problem in children than adults, although that notion has been challenged in recent years with several adult studies reporting relatively high incidence of post-extubation stridor (Cheng et al. 2006; Francois et al. 2007; Lee et al. 2007).

36.2.1 Selection of an Appropriate Endotracheal Tube

Reactive edema from endotracheal intubation has been described for many years in both children and adults (Koka et al. 1977; Stoelting and Procter 1968; Pender 1954). Moreover, given that the narrowest area of the infant and child's airway is below the vocal cords, care must be taken to ensure that an appropriate size endotracheal tube is selected before intubation. While different formulae exist for prediction of optimal tube size based on age, height, or weight, the most widely used algorithm for tube size is derived from the modified Cole formula (Cole 1957) ($[\text{age}(\text{years})/4] + 4$ mm ID) for uncuffed endotracheal tubes. In general, it is believed that when choosing a cuffed endotracheal tube, one half size smaller than predicted by the Cole formula should be selected, except for tubes of 3.0 mm ID or smaller (Deakers et al. 1994; Newth et al. 2004).

Dating back to the early days of endotracheal intubation for surgical procedures, anesthesiologists have noted less frequent complications when children were intubated with smaller size endotracheal tubes (Kaye 1936; McCarthy 1940). Because easy passage through the vocal cords does not necessarily guarantee that the tube is not compressing the subglottic mucosa, investigators noted that tubes placed where an audible air leak was appreciated at ≤ 25 cm H₂O on initial placement with the patient muscle relaxed and the head in midline position were associated with a lower incidence of post-extubation stridor (Koka et al. 1977). While the "air leak test" has subsequently been used in a multitude of different

manners as a measure of readiness for extubation with inconsistent success, the presence of an air leak immediately on intubation indicates that the tube is likely not too large. Unfortunately the presence of an air leak is dependent on head position and muscle relaxation (Finholt et al. 1985) and has poor interobserver reliability (Schwartz et al. 1993). Nonetheless, the ideal endotracheal tube is large enough to guarantee adequate ventilation (which will depend on the disease state of the individual) yet small enough to minimize compression injury in the subglottic space at the level of the cricoid cartilage.

Given the narrowest level of the pediatric airway is at the cricoid cartilage, classic anesthesiology and critical care texts advise against placing cuffed endotracheal tubes for children less than 8 years of age, although this is changing (Thompson 2006). While many young children may not need cuffed endotracheal tubes, there are several children with severe pulmonary, cardiac, or neurologic disease in which cuffed endotracheal tubes are necessary to provide adequate oxygenation and guarantee minute ventilation. There is good evidence that current iterations of high-volume low-pressure cuffed endotracheal tubes are as safe as uncuffed endotracheal tubes for all age groups if care is taken to choose the appropriate size of tube on insertion (typically 0.5 mm ID smaller than the predicted uncuffed tube, although some investigators recommend a full size smaller (Khine et al. 1997)) and if the cuff is inflated to the minimal amount necessary to guarantee adequate ventilation, still allowing for an air leak at or just above the set or generated peak inspiratory pressure (Deakers et al. 1994; Newth et al. 2004; Thompson 2006; Fine and Borland 2004).

36.3 Risk Factors for Post-extubation Stridor

36.3.1 Age

Given the anatomical differences between the small infant, child, and adult airway, it seems reasonable to suspect that the younger the child, the more likely they are to develop post-extubation

stridor. Interestingly, several investigators have noted that in fact the youngest children (<1 year) actually have a lower incidence of post-extubation stridor than older children (Koka et al. 1977), with those in the 1–5-year (Tellez et al. 1991; Deakers et al. 1994; Newth et al. 2004) age group having the highest risk. The explanation for these findings is not entirely clear, but seems to be consistent regardless of the duration of the intubation.

36.3.2 Length of Intubation

Subglottic edema may develop very quickly after endotracheal intubation (Koka et al. 1977; Stoelting and Procter 1968; Hartley and Vaughan 1993), although in general it is believed that patients who receive “prolonged” mechanical ventilation are at higher risk (Koka et al. 1977; Harrison and Tonkin 1965, 1967). Nonetheless, longer lengths of mechanical ventilation are by no means a prerequisite for the development of significant post-extubation airway obstruction. Animal models suggest that laryngeal injury from endotracheal intubation reaches its peak somewhere between 1 and 7 days of mechanical ventilation, with no real increase in injury with periods of intubation beyond 7 days (Bishop et al. 1985). While there may be no “completely safe” length of endotracheal intubation, with careful consideration of appropriate tube size, post-extubation stridor is less likely for children intubated less than 24 h. For this reason, most studies comparing potential prophylactic treatment for post-extubation stridor limit enrollment to patients intubated for >24–48 h. It is unclear, however, if the risk of post-extubation stridor continues to increase based on length of mechanical ventilation beyond 48 or 72 h (Deakers et al. 1994; Ho et al. 1996).

36.3.3 Neurologic Dysfunction

The presence of chronic or acute neurologic dysfunction has been associated with extubation failure (Kurachek et al. 2003; Harel et al. 1997). Given the differences between airway structure and control, infants and children are particularly prone to

upper airway obstruction because of poor airway tone during sleep or with CNS injury. In fact, children with underlying neurologic conditions who are intubated for longer than 48 h may be up to three times more likely to fail extubation than those without underlying neurologic abnormalities, although these failures are not all as a result of upper airway obstruction (Kurachek et al. 2003).

36.3.4 “Air Leak Test”

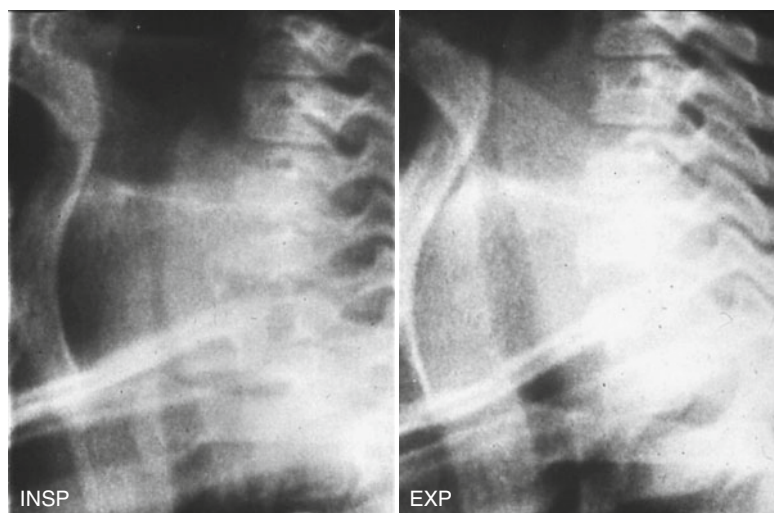
While the presence of an air leak on intubation with the head in midline position and the patient under muscle relaxation has been used to guide appropriate sizing of the endotracheal tube, applying a similar “leak test” on extubation has been described for several years with limited success. The air leak test was originally validated for children with croup, where it was found that the presence of an air leak at or below 40 cm of H₂O was more likely to predict successful extubation (Adderley and Mullins 1987). It has subsequently shown to be useful when applied to a population of pediatric trauma and burn patients (Kemper et al. 1991a). Unfortunately, there is significant interobserver variability in the assessment of a leak at extubation: it is dependent upon head position, sedation, and presence of secretions in the airway. Further attempts to validate the “leak test” prior to extubation have shown limited utility (Wratney et al. 2008; Mhanna et al. 2002), particularly for small children, although it may be more useful for older children. A single-institution retrospective study by Mhanna et al. demonstrated that for children over the age of 7 years, there were fewer episodes of stridor when there was an air leak present at or below 27 cm H₂O, although only one patient in this study required reintubation (Mhanna et al. 2002). In contrast, a recently conducted blinded prospective observational trial by Wrateny et al. clearly demonstrated that the presence or absence of a leak at or below 30 cm H₂O just prior to extubation does not aid clinical decision making regarding extubation success or failure, regard-

less of patient age (Wratney et al. 2008). Nevertheless, an “air leak” is commonly used to assess risk for extubation failure by pediatric intensivists, and many would delay extubation to administer prophylactic corticosteroids prior to extubation based on the absence of a leak (Foland et al. 2002). However, there does not appear to be compelling evidence for this practice. Practically speaking, the presence of an air leak at or below 30 cm of H₂O may be reassuring, but the absence of a leak does not reliably mean the patient is more likely to fail extubation.

36.3.5 “Cuff Leak Volume”

For patients with cuffed endotracheal tubes, the more appropriate test for a leak at extubation may be the “cuff leak volume.” During this procedure, the cuff of the endotracheal tube is inflated such that no air leak is present during inspiration. A series of 4–6 breaths are given with the mechanical ventilator, and the exhaled tidal volume measured. The cuff is subsequently deflated (with the patient sedated) and the exhaled tidal volume is measured on the same ventilator settings. The difference between the tidal volume with the cuff inflated versus deflated can be expressed as either a percentage or an absolute number. Adult studies have demonstrated that patients with a relatively high cuff leak volume (>18–24 %) have a low incidence of post-extubation stridor (Cheng et al. 2006; Lee et al. 2007; Chung et al. 2006). While the sensitivity, specificity, and positive and negative predictive value of the test vary significantly based on the study (De Bast et al. 2002; Miller and Cole 1996; Kriner et al. 2005; Jaber et al. 2003), evidence is mounting that the cuff leak volume test can identify adults at low risk of extubation failure and may be a reasonable way to define a high-risk group, based on the cutoff value that is chosen. However, no current consensus exists about what this optimal level should be (Ochoa et al. 2009), and this test has, as of yet, not been validated for use in children with cuffed endotracheal tubes.

Fig. 36.1 Lateral radiograph of dynamic obstruction during inspiration for a child with subglottic (extrathoracic) airway obstruction from malacia. Notice how the airway caliber gets smaller during inspiration and returns to normal during exhalation



36.3.6 Other Risk Factors

While no good evidence exists, other factors theorized to affect the likelihood of development of post-extubation stridor may include fluid status at or near extubation, level of sedation prior to extubation, presence of airway trauma upon intubation, number of intubation attempts, need for reintubation or other airway manipulation (Gomes Cordeiro et al. 2004), and level of activity during intubation.

36.4 Manifestations of Post-extubation Upper Airway Obstruction

Children may have respiratory insufficiency after extubation for a multitude of reasons. While post-extubation stridor has been cited as the most common cause for extubation failure (Edmunds et al. 2001), any number of other factors can lead to the common unifying presentation of respiratory distress after extubation. Moreover, the hallmark clinical finding in upper airway obstruction, stridor, is somewhat subjective and open to interpretation. While

scales have been created to assess the severity of stridor, they still may have significant interobserver variability (Deakers et al. 1994; Harel et al. 1997) and have not been validated against objective invasive or noninvasive measures of airway obstruction.

36.4.1 Clinical Signs and Symptoms

Depending on the location of the airway obstruction (extrathoracic or intrathoracic), the patient will present with flow limitation on inspiration (extrathoracic) or both inspiration and exhalation (intrathoracic). If this is limited to inspiration, then the patient will have stridor, a high-pitched inspiratory noise, and increased work of breathing with the use of accessory muscles on inspiration. If the lesion is more distal, as may be the case for significant tracheal stenosis or even distal tracheomalacia, then the stridor may be audible on both inspiration and exhalation (stertor). Because the cricoid cartilage is extrathoracic, many cases of upper airway obstruction which are a direct complication of endotracheal intubation manifest with inspiratory stridor, with little if any expiratory component (Fig. 36.1).

Further, most lesions in the extrathoracic space will manifest with similar clinical symptoms. As such, from simple clinical examination it is difficult to distinguish laryngeal edema from subglottic edema or stenosis, vocal cord dysfunction or paralysis, or laryngo- or tracheomalacia.

36.5 Quantifying the Degree and Location of Airway Obstruction

Unlike other respiratory diseases, children with significant upper airway obstruction often do not demonstrate respiratory failure on blood gas analysis (Wesley et al. 1968; Newth et al. 1972), and a normal blood gas is not necessarily reassuring if a patient has significant work of breathing. Therefore, the decision to implement further therapy or supportive measures such as intubation and mechanical ventilation is often based on clinical assessment. The addition of both invasive and noninvasive monitoring can help quantify the degree of work, the need for further therapy, and the response to a particular intervention (Argent et al. 2008a, b).

36.5.1 Pulsus Paradoxus

To maintain adequate flow, as resistance in the upper airway increases, the pressure differential between atmospheric pressure and intrathoracic pressure will necessarily have to increase. As a consequence, children with airway obstruction, at any level, will attempt to make their intrathoracic pressure more negative to ensure adequate airflow. This further decrease in intrathoracic pressure will result in increased afterload on the left ventricle by increasing left ventricular wall tension, without a significant change in LV preload. When the change in LV afterload is severe, cardiac output decreases, and the magnitude of arterial blood volume that is ejected during inspiration will decrease (Clark et al. 2004; Frey and Freezer 2001). While physiologic variation in cardiac output with the respiratory cycle is well described, when this response is exaggerated, it is

known as pulsus paradoxus and can be visible on arterial or central venous pressure waveforms, as well as noninvasive pulse oximetry (Fig. 36.2). Moreover, the degree of pulsus paradoxus has been shown to correlate with the degree of airway obstruction (Clark et al. 2004; Steele et al. 1998). However, pulsus paradoxus is not unique to upper airway obstruction and may be present as a consequence of other respiratory or cardiac disease (Wong 2007; Swami and Spodick 2003; Yalamanchili et al. 2005; Blaustein et al. 1986; Shiomi et al. 1991; Tamburro et al. 2002).

36.5.2 Spirometry: Flow Versus Volume Loops

It is often difficult to determine whether a patient has upper airway obstruction upon extubation and can be even more difficult to determine the location of the airway obstruction—extrathoracic, intrathoracic, large airways, and medium- or small-sized airways. When combined with the physical exam, spirometry can help clinicians determine the level of obstruction and quantify its severity. This can be accomplished by placing either a tight-fitting mask over the nose and mouth for young children (Bates et al. 2000; Weiner et al. 2003) during tidal breathing or an oral tube with a good seal around the lips for older, cooperative children.

Patients with an extrathoracic obstruction, like croup, vocal cord dysfunction, or subglottic reactive edema after endotracheal intubation will manifest with flow limitation on inspiration, which has a characteristic flattening of the inspiratory limb of the flow-volume loop with a normal expiratory limb (Fig. 36.3). If the lesion is intrathoracic, then the shape of the flow-volume loop depends on whether the obstruction is fixed (such as foreign body aspiration, tracheal stenosis, vascular ring) or variable (tracheomalacia). Variable lesions like tracheomalacia generally show flattening on exhalation, while fixed lesions have flattening of the loop on both inspiration and exhalation. Diseases of the lower airways (asthma and bronchiolitis) classically have flow limitation on exhalation, with a characteristic



Fig. 36.2 Pulsus paradoxus in a child with croup. Points A and B represent systolic blood pressure, while points C and D represent diastolic blood pressure. Points E and F represent the peak amplitude of the pulse-oximetry

waveform. Note that at the peak of inspiration (bottom), there is a decrease in both systolic and diastolic pressure (middle, D and B) and magnitude of the pulse-oximetry waveform (top, F)

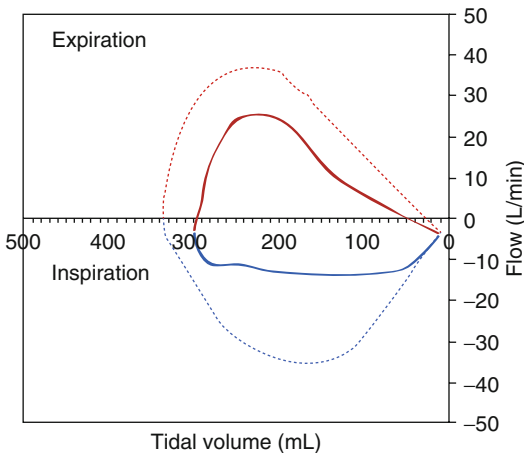


Fig. 36.3 Flow-volume loop for a child with extrathoracic airway obstruction. By convention, inspiration is negative on the Y axis and exhalation positive. Note the flattening of the inspiratory limb for the child with extrathoracic airway obstruction (solid) compared to the rounded normal (dotted) loop. Because the lesion is extrathoracic, the shape of the expiratory limb is not significantly different from a normal loop

“scooped” appearance to the expiratory limb of the flow-volume loop (Khemani et al. 2007).

36.5.3 Esophageal Manometry

Esophageal manometry has a variety of applications for titrating respiratory support and can be used as a surrogate marker for alveolar pressure and help compartmentalize compliance measurements for different components of the respiratory system (Benditt 2005). In addition, the relative change in esophageal pressure from inspiration to exhalation when combined with respiratory rate can be used as a surrogate marker for work of breathing (pressure-rate product (PRP)). While it does not directly measure work, PRP gives a relatively simple way to characterize the “effort” of breathing and correlates well with oxygen cost or metabolic work

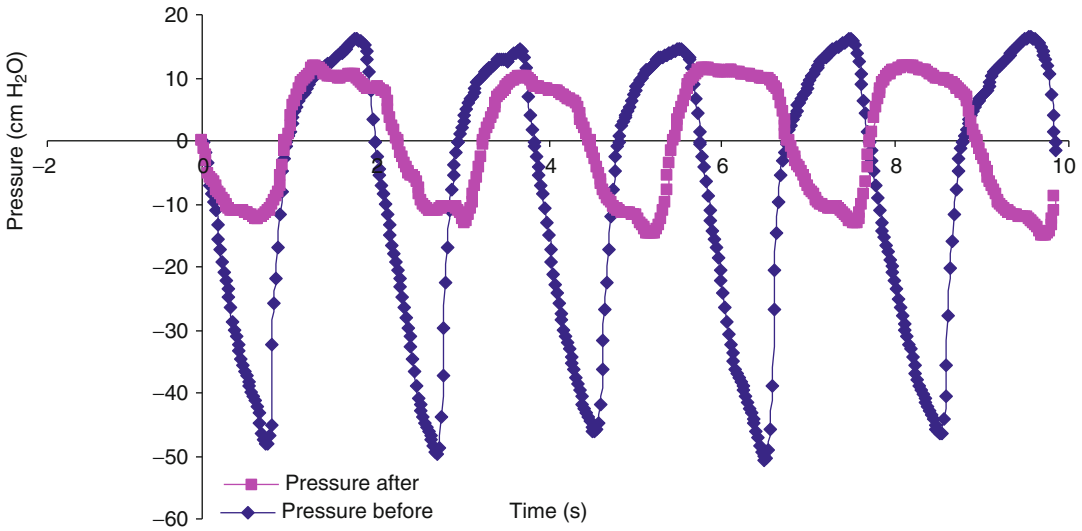


Fig. 36.4 Pressure versus time measured with esophageal manometry for a patient with extrathoracic airway obstruction from croup, before and after administration of racemic epinephrine. Note the decrease in change in

esophageal pressure (ΔP_{es}) and decrease in pressure-rate product ($PRP = \Delta P_{es} * \text{respiratory rate}$) from baseline (*blue diamond*) after racemic epinephrine administration (*pink square*)

(Collett et al. 1985). Measurement requires placement of an esophageal catheter not much larger than a feeding tube into the lower third of the esophagus to measure intrathoracic swings in pressure (Fig. 36.4). The technique has been successfully applied to both infants and older children (Argent et al. 2008a, b; Graham et al. 2007; Willis et al. 2005; Klein and Reynolds 1986). While it does not distinguish the area of obstruction, it does quantify the respiratory effort and can be combined with spirometry to demonstrate inspiratory flow limitation with continual respiratory effort. A patient with extrathoracic airway obstruction (such as post-extubation stridor from reactive edema) will have a very characteristic pattern of flow and pressure (Fig. 36.5).

36.5.4 Respiratory Inductance Plethysmography

During normal tidal breathing, diaphragm contraction leads to inspiration, followed quickly by chest wall muscle activity. However, as respiratory pathology develops, there is often an

increasing amount of thoracoabdominal asynchrony (TAA). This TAA can be characterized with respiratory inductance plethysmography in which elastic bands with an imbedded wire are placed around the rib cage and abdomen. A current is passed through the bands, which generates a magnetic field. The act of breathing alters the cross-sectional area of both the rib cage and abdominal components, thus altering the shape of the magnetic field generated by the bands. A computer can analyze this current and generate the phase angle, which is the degree of synchrony between the abdomen and rib cage, and the direction of the loop (Fig. 36.6) (Prisk et al. 2002). Studies on children with upper airway obstruction from croup (Sivan et al. 1990; Davis et al. 1993), as well as animal studies (Hammer et al. 1995), have demonstrated that the degree of TAA increases as the severity of UAO worsens. As such, phase angle measurements may serve as an objective measure to quantify the severity of airway obstruction and monitor response to interventions (Fig. 36.7). This technique offers the advantage of being completely noninvasive, unlike esophageal manometry. It is, however, not specific for UAO.

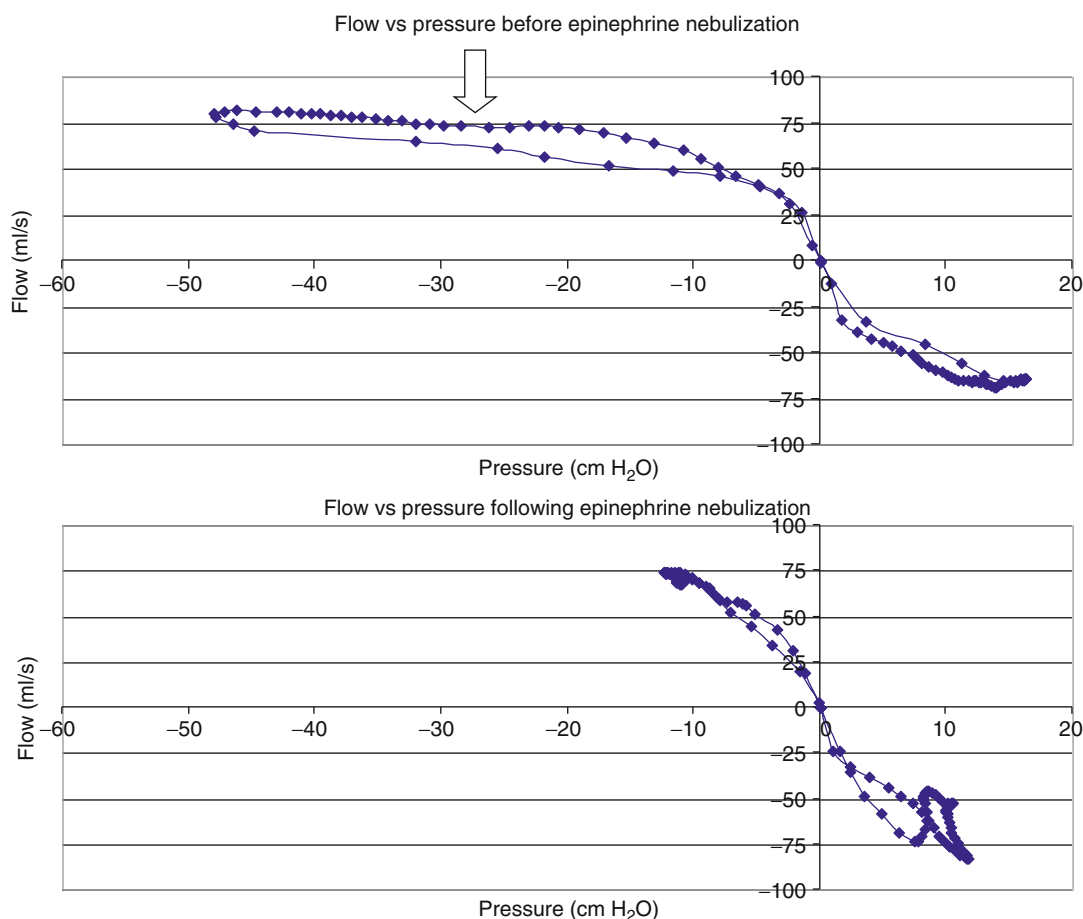


Fig. 36.5 Flow-pressure curve for a child with extrathoracic airway obstruction from croup, before and after racemic epinephrine. The flow and pressure curves show inspiration on the left of the origin and exhalation on the right. Before epinephrine (*top*) there is flow limitation on

inspiration as there is a continued decrease in esophageal pressure with no increase in flow (*left of arrow*). After epinephrine (*bottom*), flow increases and terminates without ongoing decreases in pressure

36.5.5 Endoscopy

While clinical estimates of post-extubation stridor may range from 6 to 30 %, endoscopic abnormalities may be present in up to 90 % of patients after extubation (Gomes Cordeiro et al. 2004). Single-institution studies have demonstrated that up to 50 % of infants and children may have minor changes such as edema, hyperemia, or mucosal erosion. Moderate lesions were seen in approximately 30 % of patients, including subglottic edema, vocal folds edema, ulceration, granulation tissue, or cartilaginous changes. Severe lesions including airway granulomas,

subglottic stenosis, or vocal cord paresis were present in up to 10 % of patients. Of note, the reintubation rate secondary to upper airway obstruction was close to 25 % in this population, higher than most other centers. The long- and short-term clinical implications for such endoscopic findings are unclear, although other reports seem to indicate that children who suffer simply from airway edema seen on endoscopy continue to heal after extubation, while children with more severe airway abnormalities including tracheomalacia, vocal cord dysfunction, or subglottic stenosis may have more long-term morbidity (Lin et al. 2002).

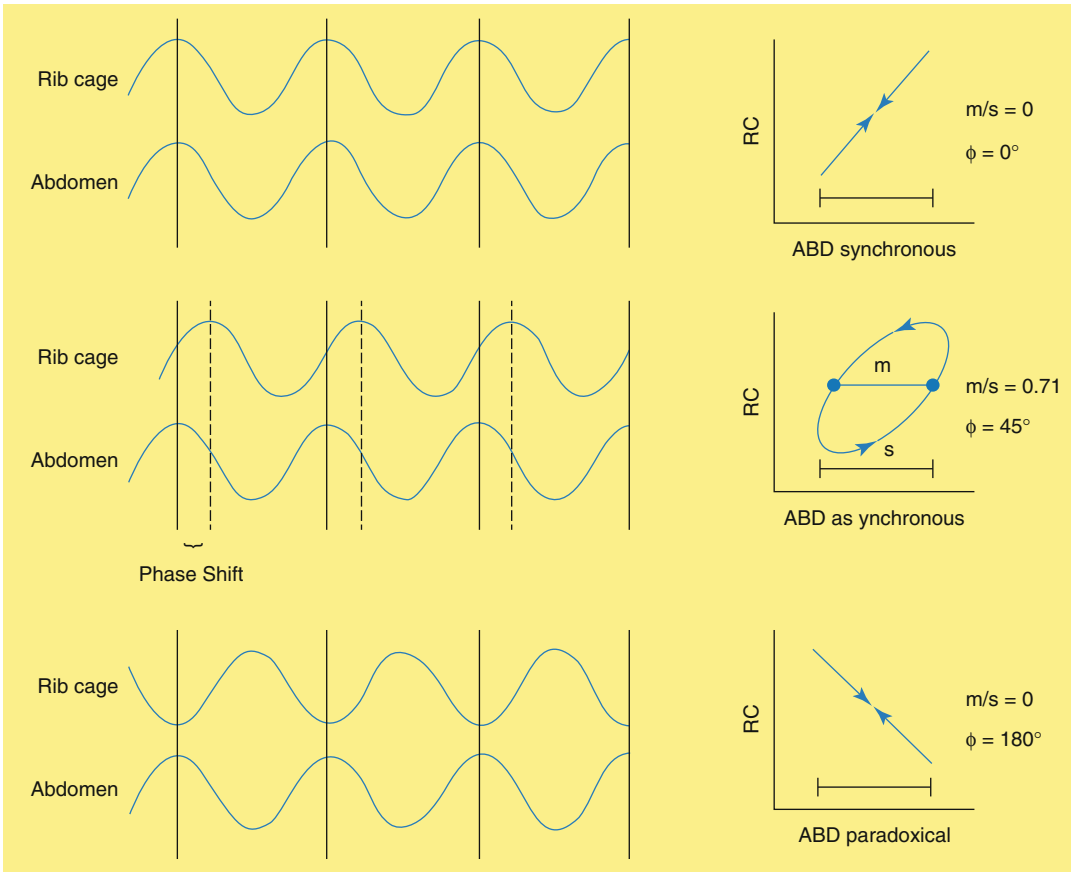


Fig. 36.6 Respiratory inductance plethysmography. Oscillatory waves are generated from the bands on the rib cage and abdomen. The phase angle is the arcsin [(width of the loop at the midpoint of the rib cage excursion)/(excursion of the abdomen)]. Under normal circumstances, the abdomen leads, followed very shortly by the rib cage, represented by a very small phase angle (Φ) with a very tight loop (*top*) and a counterclockwise rotation.

With more asynchrony between the abdomen and rib cage, the phase angle will become larger, and the loop will take on a wider appearance (*middle*), although the direction of the loop remains counterclockwise. With complete paradoxical breathing (such as bilateral diaphragm paralysis), the rib cage and abdomen are exactly 180° out of phase, with clockwise movement of the loop with the rib cage leading

36.6 Treatment and Prevention

36.6.1 Racemic Epinephrine

Racemic epinephrine has been used for many years for the treatment of acute infectious croup (Argent et al. 2008b; Westley et al. 1978; Kuusela and Vesikari 1988; Waisman et al. 1992). The mechanism of action is thought to be related to stimulation of alpha adrenergic receptors, causing local vasoconstriction in edematous mucous membranes, decreas-

ing vasogenic edema. Because of its benefit in infectious croup, racemic epinephrine has been used to treat post-extubation stridor, although little formal evaluation of its use to prevent reintubation from upper airway obstruction has been done (Argent et al. 2008b; Davies and Davis 2002), with no randomized clinical trials. Nonetheless, in its nebulized form, it is commonly used in pediatric intensive care units for the treatment of post-extubation stridor. It can also be nebulized with the aid of continuous or intermittent noninvasive positive

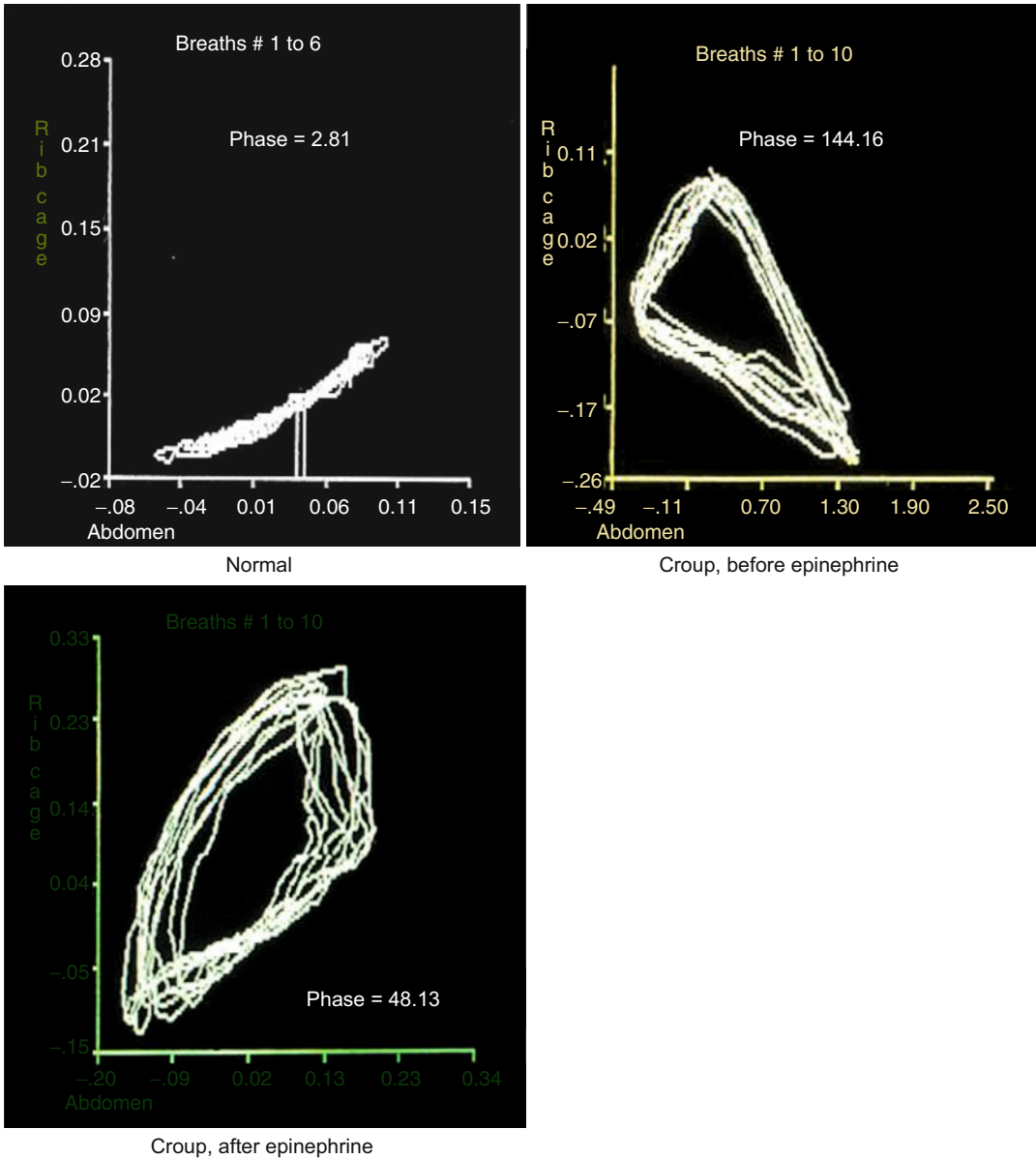


Fig. 36.7 Phase angles from respiratory inductance plethysmography for a child with upper airway obstruction from croup, before and after racemic epinephrine. Note that in the normal situation (*top left*), the abdomen and rib cage are synchronous, with a tight loop with a very small phase angle (phase = 2.81°). In the child with

croup (*top right*), before administration of racemic epinephrine, there is more asynchrony, with a wide loop, and a large phase angle (144.16°). After racemic epinephrine (*bottom left*), the phase angle improves although the loop is not completely normal (48.13°) (Adapted from Sivan et al. (1990))

pressure ventilation or vaporized with high-flow humidified nasal cannula for continuous administration in the spontaneously breathing child (Obrien et al. 2007).

36.6.2 Heliox

Helium/oxygen mixtures can be delivered continuously via nasal cannula to improve laminar flow.

Because the molecular weight of helium is lower than nitrogen, helium/oxygen mixtures can decrease the relative density of the gas mixture in a pipe (trachea), and lower the Reynolds number. When the Reynolds number is $<2,300$, flow is laminar, with lower airway resistance. Heliox has been shown to be effective in infectious croup (Weber et al. 2001) and can also help treat post-extubation stridor, although studies have typically been performed in specific pediatric subgroups such as burns (Rodeberg et al. 1995) or trauma (Kemper et al. 1991b).

36.6.3 Noninvasive PPV

Noninvasive positive pressure ventilation, through the form of nasal or mask continuous positive airway pressure (CPAP), bi-level support (BIPAP), or high-flow humidified nasal cannula, may prevent reintubation secondary to post-extubation stridor, when the upper airway obstruction is relatively mild (Ito et al. 2006; Sundaram and Nikolic 1996; Chantarojanasiri et al. 1993; Wang et al. 1996; Byerly et al. 2006). The mechanism of action is likely related to stenting of the upper airway with positive pressure and may facilitate delivery of medications, such as epinephrine. However, there has been no systematic assessment of the utility of such therapies, and their use has mostly been described in case reports.

36.6.4 Reintubation

When upper airway obstruction after extubation proves severe and does not respond to other non-invasive therapies such as racemic epinephrine, heliox, or noninvasive ventilation, reintubation may be necessary. It is generally believed that upon reintubation, a smaller endotracheal tube should be placed, again with care taken to ensure that an adequate air leak is present upon intubation with the head in midline position and the patient muscle relaxed. While many practitioners may place these patients on prophylactic corticosteroids before another extubation attempt, this

practice has not been proven either effective or necessary (Harel et al. 1997).

36.6.5 Corticosteroids

On the grounds that the reactive edema which develops around an endotracheal tube may improve with the aid of anti-inflammatory agents, systemic corticosteroids have been used to try to treat or prevent post-extubation stridor for many years. While there has yet to be an adequately powered randomized controlled trial addressing the use of steroids to prevent post-extubation stridor in neonates or children (Tellez et al. 1991; Anene et al. 1996; Courtney et al. 1992; Couser et al. 1992; Ferrara et al. 1989), there is evidence that corticosteroids may be beneficial to prevent post-extubation stridor for “high-risk” children, particularly if given as multiple doses begun 12–24 h prior to extubation (Anene et al. 1996; Tibballs et al. 1992; Markovitz et al. 2008). However, there is not adequate evidence that reintubation from upper airway obstruction can necessarily be prevented with prophylactic corticosteroids. Unfortunately, the data for children are limited to only a few randomized controlled trials, which have significantly different results. The trials in neonates and children which have shown a benefit for steroids included children with underlying airway anomalies, multiple intubations, or airway trauma (Anene et al. 1996; Couser et al. 1992). While any corticosteroid could theoretically be used, dexamethasone given intravenously for 4–6 doses at 0.25–0.5 mg/kg/dose appears to be most accepted for infants and children (Markovitz et al. 2008).

There is growing evidence that for adults multiple doses of corticosteroids begun 12–24 h prior to extubation are beneficial to prevent post-extubation stridor and may be beneficial to prevent reintubation from airway obstruction, particularly if the patients are in some way “high risk” (Cheng et al. 2006; Francois et al. 2007; Lee et al. 2007; Markovitz et al. 2008; Khemani et al. 2009). Most “high-risk” criteria in adults involve patients who are intubated for a minimum of 24–48 h and fail certain cuff leak volume criteria ($<24\%$, or <110 ml).

Unfortunately, characterizing “high risk” in infants and children is a bit more challenging, particularly given that objective measures of upper airway obstruction are not routinely used in clinical practice. While several potential risk factors exist for the development of post-extubation stridor (see above), few if any of them have been evaluated prospectively to help define a high-risk cohort in which corticosteroids may be of more benefit. Further, given the clear differences in airway structure, anatomy, and intubation and ventilation practices between adults and children, extrapolating adult evidence regarding the use of corticosteroids to children or neonates is not warranted. However, future studies that address the issue of corticosteroids for the prevention of reintubation secondary to upper airway obstruction in neonates and children should employ objective criteria to identify high-risk groups and employ treatment regimens with multiple doses of corticosteroids begun 12–24 h prior to extubation.

36.7 Long-Term Complications of Endotracheal Intubation

With the growth of the use of endotracheal intubation and mechanical ventilation in the 1970s–1990s, the incidence of severe airway complications such as subglottic stenosis rose considerably, with rates ranging from 0.8 to 8 % (Wiel et al. 1997; Grundfast et al. 1990; Puhakka et al. 1990). With greater attention to appropriate tube sizing and sedation during intubation, there appear to be fewer reported cases of subglottic stenosis in the literature, although there has been surprisingly little published in the last several years. Nonetheless, even with great care and safe intubation practices, some children will still develop severe subglottic stenosis which may require further surgical consideration or tracheostomy. Other rare complications reported include neuromuscular dysfunction with tongue drop, laryngotracheal incoordination, saliva pooling over the larynx with poor cough reflex, laryngomalacia, tracheomalacia, airway granulomas, and vocal cord paralysis (Lin et al. 2002; Martins et al. 2006).

Essentials to Remember

- Complications of post-extubation airway obstruction can be minimized by careful selection of an appropriate endotracheal tube. While population-based formulae should be used as a guide, endotracheal tube size should be personalized for the patient by assuring an appropriate air leak on initial placement.
- Cuffed endotracheal tubes can be as safe as uncuffed endotracheal tubes, as long as care is taken to assure the tube is of appropriate size on initial placement. In addition, the cuff should only be inflated to the minimal amount necessary to guarantee adequate ventilation, still allowing for an air leak at or just above the set or generated peak inspiratory pressure.
- The extubation air leak test has not been reliably associated with increased likelihood of extubation failure. While the presence of an air leak at or below 30 cm of H₂O may be reassuring, the absence of a leak does not reliably mean the patient is more likely to fail extubation and should not delay extubation.
- Clinical acumen regarding stridor severity is poor, with significant interobserver variability. Objective measures of airway obstruction such as spirometry combined with esophageal manometry or respiratory inductance plethysmography combined with esophageal manometry should be further developed. This will help identify reliable risk factors, potential therapies, and preventative measures.
- Routine use of prophylactic corticosteroids does not prevent post-extubation stridor. Future investigation is needed to define high-risk groups for which steroids may be beneficial. It appears as if single doses of steroids begun shortly before extubation are not helpful, so future investigations should examine multiple repeated doses of corticosteroids begun 12–24 h prior to extubation.

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Part XII

Bronchoscopy in Pediatric and Neonatal Intensive Care

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Educational Goals

- To understand the benefit of being able to perform flexible and rigid bronchoscopy in the ICU for lifesaving, diagnostic, and therapeutic purposes in ventilated infants and children
- To know the safety requirements, the risk factors, and the complications of bronchoscopy in the ICU

37.1 Introduction

Since the introduction of the flexible bronchoscope by Ikeda in 1968 (Ikeda 1968), technical refinements of the equipment have greatly facilitated its use in the care of critically ill children on invasive mechanical ventilation. The ever-thinner instruments allow performing bronchoscopy through endotracheal tubes (ETT) as thin as 2.5 mm in internal diameter, and the procedure has become a valuable tool for various diagnostic purposes and

therapeutic measures in intensive care. Despite the apparent simplicity of the procedure, flexible bronchoscopy in the critically ill should be performed by the experienced bronchoscopist in an expeditious and deliberate manner, with assisting personnel paying close attention to vital parameters. The secured airway and the preestablished sedation may create a treacherous sense of security, and distraction caused by captivating events and findings on the screen, pointedly referred to as the “bronchoscopy hypnosis” (Wood 1990), carries the risk of subtle signs of cardiorespiratory instability going unnoticed and precipitating into a serious critical incident. With due respect to the potential risks, however, bronchoscopy is astoundingly safe in even the sickest patients.

37.2 Physiological Effects and Complications of Bronchoscopy

The introduction of the flexible bronchoscope into the ETT causes an abrupt increase of the flow resistance, caused by the reduction of its internal cross-sectional area and, in general, by the disruption of the laminar flow within the tube. Cardiorespiratory stability of the patient may be further jeopardized by suctioning (Arai et al. 1985), partial blockade of airways, vagal stimulation, and, if inevitable, the temporary disconnection of the patient from the ventilator.

Earlier studies examining adverse effects of flexible bronchoscopy in spontaneously breathing

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patients concentrated on its impact on gas exchange, reporting a usually mild decrease of the arterial oxygen partial pressure (PaO_2) by 10–20 mmHg during the procedure (Albertini et al. 1974; Schnapf 1991; Franchi et al. 1993; Ghows et al. 1986; Randazzo and Wilson 1976; Dubrawsky et al. 1975; Kleinholz and Fussel 1973). Severe hypoxemia with $\text{SpO}_2 < 80\%$ is a rare event occurring in less than 1 % of individuals undergoing bronchoscopy (Nussbaum 2002). Later work chronologically associated these events with a significant drop of maximum flow rates in the order of one fourth to one third after introducing the instrument into the lower airways (Matsushima et al. 1984). A concomitant elevation of the functional residual capacity (FRC) may counteract the oxygen desaturation (Matsushima et al. 1984; Craig et al. 1971).

Air flow is significantly more impeded when the procedure is performed via an ETT as compared to the transnasal route (Matsushima et al. 1984). It has been calculated that, while inserting a 5.2 mm instrument into an 11-mm-wide trachea would increase airway resistance about twofold, introducing the same instrument into an 8.0 mm ETT would augment airway resistance as much as 11-fold (Matsushima et al. 1984). A similar five- to sixfold increase was calculated by others for the introduction of a 1.8 mm ultrathin instrument into a 3.0 mm neonatal ETT (Vigneswaran and Whitfield 1981). More recent studies in *ex vivo* models correlated the changes of air flow dynamics and ventilatory parameters with various combinations of ETT sizes and bronchoscope dimensions during mechanical ventilation, demonstrating that tidal volumes may drop dramatically under pressure-controlled ventilation (Hsia et al. 2009; Lawson et al. 2000). In the volume-controlled mode, tidal volumes are preserved but peak inspiratory pressures may increase up to >20 cm H_2O (Lawson et al. 2000). A high-pressure limitation, again, will affect tidal volumes. The pressure gradient over the ETT will not allow full transmission of the increased peak pressures into the pulmonary periphery, but partial obstruction of the ETT is associated with increasing auto-positive end-expiratory pressures (auto-PEEP) in

volume-controlled modes, particularly with the high respiratory rates used in children (Lawson et al. 2000). As a consequence, a minimum ETT to bronchoscope diameter difference of 1.3 mm has been recommended for infants and toddlers, 2.0 mm for children, and 2.5 mm for adolescents (Hsia et al. 2009).

As the increase in airway resistance must be met with enhanced work of breathing, patients with limited muscle strength or with cardiac failure are more likely to show hypoventilation during flexible bronchoscopy. Anesthesia attenuates counter-regulatory mechanisms. At least in the short run, even healthy children may not fully compensate for the increased airway resistance imposed by the instrument (Trachsel et al. 2005). Unsurprisingly, critically ill patients are particularly vulnerable to oxygen desaturation during the procedure (Peerless 1996; Papazian et al. 1993; Montravers et al. 1993; Trouillet et al. 1990), and active bronchospasms may result in an additional resistive burden.

In addition to the respiratory effects, flexible bronchoscopy and in particular bronchoalveolar lavage (BAL) may adversely affect hemodynamic stability of critically ill patients. Arrhythmias seem to rarely occur if oxygen saturation is maintained during the procedure (Trouillet et al. 1990; Katz et al. 1981). Studies in mechanically ventilated adults, however, suggest that cardiac output slightly increases in most patients during bronchoscopy but that the risk of hypotension increases in relation to disease severity (Papazian et al. 1993; Montravers et al. 1993; Trouillet et al. 1990). Flexible bronchoscopy with BAL may provoke bouts of pulmonary arterial hypertension with increased right ventricular stroke work (Bein et al. 1995). Auto-PEEP as well as the increased pulmonary vascular resistance augment central venous pressures and thereby impede cerebral blood outflow. A significant increase of the intracranial pressure (ICP) was found in 4/5th of adult patients with brain injury (Kerwin et al. 2000). In this study, cerebral perfusion pressure was preserved by a concomitant increase of the arterial pressure, and no adverse effect on neurological outcome due to the cardiovascular changes during bronchoscopy

was suspected. Time to reversal of intracranial hypertension was 10–15 min.

37.3 Technical and Practical Aspects of Bronchoscopy in Ventilated Patients

37.3.1 Equipment

Flexible bronchoscopes are categorized as fiber-optic, video, or hybrid bronchoscopes. The newer video bronchoscopes feature a charge-coupled device (CCD) chip at the tip of the bronchoscope that transfers the image electronically to a proximal processor, allowing higher resolution and thus superior images compared to optically transmitted images of fiber-optic bronchoscopes (Yoneda and Morrissey 2008). The smallest video bronchoscope currently has an outer diameter of 3.8 mm. Hybrid bronchoscopes transmit the images optically to a CCD located in the proximal head of the instrument. Manufacturers provide monitors and suitable recording media for documentation of bronchoscopic findings. Apart from legal requirements of documentation, video recording allows to review the endoscopic findings post-procedurally, both for teaching purposes and for interdisciplinary case discussions.

Flexible fiber-optic instruments are preferable to rigid bronchoscopes for most indications of bronchoscopy in childhood, particularly functional studies of airway collapsibility and bronchoalveolar lavages (BAL). Rigid bronchoscopes secure instable airways and allow better ventilatory support and instrumentation. Ultrathin instruments are useful in very small neonates when visualization of the airways through a ≤ 3 mm ETT is necessary. Downsides of these bronchoscopes are the absence of a suction channel and that the optical fibers in these delicate instruments easily break even with cautious handling.

Bronchoscopy in the intensive care unit is rarely feasible without ventilatory assistance. Ventilatory masks that allow simultaneous bag-mask ventilation should be used in non-intubated patients (Frei et al. 1995). If the airway is secured

with a laryngeal mask airway (LMA) or an ETT, a swivel adapter can be utilized for ventilatory support during the procedure.

If bronchoscopy is performed through an ETT, it is advisable to apply silicone or a similar lubricant onto the instrument, or at least moisten it with normal saline. It is typically easier to push a bronchoscope through a narrow ETT than to pull it out again. Forceful extraction may cause ETT dislocation or damage to the airways and the instrument. In addition, the proximal ETT adapter is sharp-edged and frequently the narrowest part of the ETT. It is easy to damage the tip of the scope if the instrument is forced through it, and removal of the ETT adapter might be necessary for the procedure which will then have to be performed in apnea or spontaneous breathing, respectively.

37.3.2 Safety (Prerequisites) and Monitoring

The most important element of monitoring is an assisting person designated to supervise patient and monitors. Pulse oximetry is a condition *sine qua non*, and sicker patients should be monitored via all preestablished modalities including ECG, blood pressure, and ICP measurements. An appropriately sized mask should be at hand in case of inadvertent ETT dislocation, and the drugs chosen for potential reintubation should be determined.

37.3.3 Sedation and Analgesia

Type of sedation and analgesia chosen for bronchoscopy varies according to the patient's individual risk profile and to local preferences (Berkenbosch et al. 2004; Slonim 1999). Although serious cardiac arrhythmias are rarely provoked by bronchoscopy, having a defibrillator in the vicinity seems prudent in patients at risk for cardiovascular complications. Atropine for vagal depression and a catecholamine for immediate cardiovascular support should be at hand for timely intervention.

In view of the potential risks associated with flexible bronchoscopy in critically ill patients, experts recommend the procedure to be accomplished as expeditiously as possible and that patients should be oxygenated and well sedated for the intervention. Some may even benefit from neuromuscular blockade to eliminate agitation and cough (Hertz 1993). Patients with preexisting pulmonary arterial hypertension may be particularly at risk for adverse hemodynamic effects.

37.4 Indications for Bronchoscopy in the NICU/ PICU

37.4.1 Diagnostic Indications

37.4.1.1 Patency and Position of Endotracheal Tubes

Accidental migration of endotracheal tubes (ETT) has been recognized as an important morbidity factor in ventilated children, and malposition is a common event despite clinical evidence of correct placement (Phipps et al. 2005; Harris et al. 2008). Auscultation methods have their limitations as well (Verghese et al. 2004), and no clinical technique results in 100 % success. Flexible endoscopy allows for quick visualization of tube position, which is especially useful in critical situations when there is not enough time to wait for chest radiography. There are clinical or anatomical circumstances where exact ETT position is of critical importance for patient management (Soong 2004; Sripada et al. 2008; Lucking-Famira et al. 2004). Correct positioning of the tube can be immediately confirmed. In contrast to radiological imaging, it has the advantage that it can be repetitively performed in case of doubt. Fiber-optic assessment of ETT position is often used in studies evaluating new tubes in children (Weiss et al. 2005; Jordi Ritz et al. 2008). Portable battery bronchoscopes offer a very convenient solution for such purposes (Angelotti et al. 2006).

There are many causes of ETT obstruction, including kinking, tube defects, foreign body obstruction, secretions, tracheal mucosal flaps,

blood clots, and even parasitic infections (Leissner et al. 2007; Xue et al. 2009). Fiber-optic bronchoscopy may be helpful to examine the artificial and human airway in case of suspected endotracheal tube obstruction or central airway obstruction (e.g., from tracheomalacia (Oh et al. 2002), abnormal thoracic configuration (Donnelly and Bisset 1998), etc.), if this can be safely and quickly performed.

37.4.1.2 Evaluation of Tracheostomy

Tracheostomy tube size is described most commonly in terms of the internal diameter. The curvature and length of the tracheostomy tube should be appreciated when selecting a tube for any given child, as it will vary between different designs and manufacturers. While the trachea is essentially straight, some tube designs have a curvature that does not permit a parallel alignment which may lead to the tracheostomy tip becoming compressed against the anterior tracheal wall causing partial obstruction. A longer proximal length may be required in obese patients, while additional distal length may be useful in patients with anatomical abnormalities of the tracheal wall, e.g., tracheomalacia.

Fiber-optic bronchoscopy is an important tool to assess the airways of children with a chronic tracheostomy comprising a relevant patient population in many pediatric intensive care units (Carr et al. 2001; Marcin et al. 2001). Tube complications such as tube obstruction, bleeding, or stomal granulomas can be easily detected. Bronchoscopic assessment of the airway should be routine prior to any decannulation trial in children with long-term tracheostomies. Special attention has to be given to assure unobstructed upper airway function during spontaneous breathing before decannulation of such children.

37.4.1.3 Assessment of the Upper Airway (e.g., Pre- and Postintubation, Upper Airway Obstruction, Smoke Inhalation, Burn Injury)

Endoscopic examination of the upper airway and assessing its proper function can be important and lifesaving in critically ill children. Children

with postextubation stridor may require endoscopy to assess the extent and the exact nature of their airway lesion such as subglottic edema, laryngeal injury, or vocal cord palsy. Early visualization of postextubation stridor is recommended after thoracic procedures, in neurological disorders associated with intracranial hypertension or after extubation failure possibly due to intubation trauma or the use of inappropriately sized tubes. Endoscopic assessment of the upper airway may also provide helpful information prior to extubation of children with critical airways. Under certain circumstances, it may be wise to extubate while simultaneously assessing proper upper airway function by fiber-optic laryngoscopy. This will also allow immediate fiber-optic reintubation in case of instant extubation failure. In the experience of the authors, this is facilitated by using an endoscopy mask, by which CPAP and manual ventilation can be instantaneously applied to prevent respiratory deterioration (Erb et al. 1997; Hammer et al. 2001). In children with such critical airways, we perform fiber-optically controlled extubations using a short-acting sedative (such as propofol) after they have been weaned off long-acting sedatives. It is important that all tools for difficult airway management are at the bedside.

Traumatic supraglottitis may occur after mechanical, thermal, chemical, or other airway injury. Children in whom traumatic epiglottitis is suspected should be approached with the same caution and preparedness for emergency airway management and intensive care as those with acute infectious epiglottitis. The same principles may not only apply to intubation but also to extubation of these children. Equipment has to be prepared for flexible and rigid bronchoscopy and emergency tracheostomy. Depending on the local setup and experience, this may be done in the intensive care unit, in the operating room, or in an endoscopy suite. More importantly, the best trained team in airway management and endoscopy should be available. The duration of intubation and the possible need to look at the airway prior to extubation are related to the underlying etiology of illness, concomitant injuries, and severity of trauma. These principles are intended

to optimize the safety and protection of the patient and may require modifications based on particular circumstances and resources (Kulick et al. 1988; Rosen et al. 2000; Deutsch 2004). Similar approaches may be required to guide extubations of children after laryngotracheal or craniofacial surgery.

37.4.1.4 Assessment of the Lower Airway (Trauma, Anastomosis, Malformations, Malacia, Tracheostomy, Tracheoesophageal Fistula (TEF), Stent Assessment)

Bronchoscopy may be helpful to assess and diagnose lower airway malformation such as an abnormal tracheal bronchus causing persistent upper lobe atelectasis (Ashmeade and Carver 2009) or tracheal or bronchial stenosis. Tracheobronchoscopy is recommended for babies with esophageal atresia before surgical repair to define the presence, the number, and the location of the fistula or to detect associated malformations of the respiratory tree (Atzori et al. 2006). Such evaluation is preferably done by rigid bronchoscopy because the airway can be maintained and ventilation can be controlled during the procedure. Endoscopy may be helpful to guide temporary occlusion of the TEF to facilitate positive-pressure ventilation of noncompliant premature lungs before surgical closure (Lucking-Famira et al. 2004; Filston et al. 1982).

Airway problems occurring after TEF repair should be investigated by endoscopy with a low threshold. Refistulation and dehiscence of anastomosis are among the postoperative complications that may require prompt diagnosis and intervention to prevent further problems. The use of methylene blue may successfully demonstrate refistulation by applying dye to the esophageal or tracheal opening of the fistula and visualizing its appearance on the opposite side. Endoscopic repair of recurrent TEF using a diathermy electrode and tissue fibrin glue has been described as an effective and safe alternative to second thoracotomy and open surgical repair (Richter et al. 2008; Meier et al. 2007). Another complication is the remnant of a tracheal diverticulum after TEF

repair. These are thought to be rare but may be the cause of significant airway problems such as difficulty in intubation, respiratory obstruction, and inability to provide effective ventilation. Airway compression can also result from expansion of the diverticulum when positive pressure is delivered by assisted ventilation (Cheng and Gazalli 2008).

Tracheomalacia (and bronchomalacia) may be a cause for persistent ventilatory requirement, failure to wean, and extended intensive care unit stay. This primarily pertains to three clinical entities: preterm infants with bronchopulmonary dysplasia, children with tracheoesophageal malformations, and children with major aortopulmonary vascular malformations (Austin and Ali 2003). Tracheomalacia may also cause cyanotic spells and life-threatening events due to airway collapse or progressive respiratory deterioration due to dynamic hyperinflation (Doull et al. 1997). Failure to wean together with suspected upper airway anomalies requires structural and dynamic assessment of the airways by endoscopy and/or radiographic investigations such as tracheobronchography or angio-computer tomography (Briganti et al. 2005; MacIntyre et al. 1998). Dynamic assessment of the trachea and bronchi, with demonstration of collapse of the airway in expiration, is often done by flexible bronchoscopy. This may be difficult in patients with borderline lung reserve and small airway diameter and has potential limitations, such as splinting of the lesion by the bronchoscope or positive airway pressure. It has been argued that bronchography is superior to endoscopy to assess dynamic airway behavior in critically ill ventilated children (MacIntyre et al. 1998; Bramson et al. 1993; Mok et al. 2005).

Tracheal or bronchial anastomosis (e.g., after lung transplantation or tracheal surgery) can be easily examined by fiber-optic bronchoscopy to assess healing or to detect and eventually treat stenosis, malacia, and dehiscence (Chhajed et al. 2001). Tracheobronchial disruption is a rare, life-threatening injury after blunt thoracic trauma in children and not a problem that is usually assessed in an intensive care unit. Pneumomediastinum after blunt trauma in clinically stable children is

rarely associated with significant underlying injury (Neal et al. 2009). Suspicion should be high when pneumomediastinum and pneumothorax are refractory to adequate pleural drainage. Flexible bronchoscopy with intubation distal to the injury may be necessary to prevent loss of the airway. Patient survival after tracheobronchial disruptions depends on skillful and creative airway management, careful diagnostic evaluation, and prompt surgical intervention (Probst et al. 2009; Grant et al. 1998).

37.4.1.5 Pneumonia (BAL in VAP, Immunocompromised Host)

Ventilator-associated pneumonia (VAP) is a common complication of invasive ventilation, and it is notoriously difficult to diagnose. Radiological differentiation between inflammatory consolidation and atelectasis is unreliable at best, and pulmonary opacifications may represent aspiration or hemorrhage which are not per se an indication for antibiotic therapy. Diagnosis of VAP is thus based on a number of clinical criteria and, ideally, cytological and microbiological analysis of airway secretions (Principi and Esposito 2007). The difficulty of interpreting such results, however, arises from the rapid colonization of the tracheal mucosa with oropharyngeal flora in a majority of intubated patients (Ewig et al. 1999; Sirvent et al. 2000). Repetitive downward leakage of secretions pooled above an ETT cuff, biofilm formation on the ETT surface, mucosal damage, and impedance of mucociliary clearance all contribute to colonization of lower airway secretions (Pneumatikos et al. 2009).

Bronchoalveolar lavage is being advocated as preferred method of sample acquisition in children with suspected VAP. One half to 1 mL/kg of normal saline, up to a maximum of 20 mL, is usually instilled, either blindly or under visual bronchoscopic control. If bronchoscopy is being performed in the non-intubated patient, aspiration of upper airway secretions with the bronchoscope should be avoided in order to prevent contamination of the suction channel. Taking samples by a protected brush technique may limit contamination from the suction channel of the bronchoscope (Wimberley et al. 1979).

In children, the brush technique may be utilized blindly through the ETT, if the suction channel of the pediatric bronchoscope is too small for the brush catheter (Labenne et al. 1999). No method so far has been proven superior with regard to patient outcome (Ramirez et al. 2007). For the differentiation of true infection from contamination, a threshold of ≥ 4 colony-forming units (cfu) per mL BAL fluid in the bacterial cultures is a commonly accepted criterion, and cytological examination showing ≥ 1 –5 % of phagocytes containing intracellular bacteria corroborates a positive result (Principi and Esposito 2007; Labenne et al. 1999). Dilution effects, inhomogeneity of lung disease, and pretreatment with antibiotics, however, inherently render any quantification unreliable (Fujitani and Yu 2006). Reported accuracy of BAL for the diagnosis of VAP varies widely among studies, with sensitivities and specificities ranging from 19 to 87 % and from 31 to 100 %, respectively (Rea-Nato et al. 2008). Thus, the major benefit of microbiological investigations of lower airway samples may be the discontinuation of unnecessary antibiotic treatment (Ramirez et al. 2007).

Newly appearing infiltrates on the chest X-ray of an immunocompromised patient, particularly in a stem cell or bone marrow transplantation (HSCT/BMT) recipient, mandate a decisive and timely work-up (Forsl w et al. 2010; Shannon et al. 2010). Infection is the most frequent culprit, and given the susceptibility of the host for a myriad of pathogenic and opportunistic agents, identification of the responsible agent is adamant for targeted therapy, not least in order to reduce the burden of drug toxicity. The diagnostic yield of BAL depends on previous anti-infective treatment, type of infection, and delay of BAL from onset of disease, varying between 30 and 70 % in various studies (Forsl w et al. 2010; Shannon et al. 2010; Huaranga et al. 2000; Kasow et al. 2007). Accuracy is better for bacteria and less so for cytomegalovirus, fungi, and noninfectious causes (Kasow et al. 2007). In severely ill patients, BAL is often delayed for fear of worsening respiratory failure. There is an undoubted potential for a patient with respiratory failure on noninvasive positive-pressure ventilation

(NIPPV) to progress and require endotracheal intubation and IPPV after BAL; the risk, however, seems reasonably low (<10 %), and fear of exacerbation likely is not a good counselor in this situation (Efrati et al. 2007; Peikert et al. 2005; Armenian et al. 2007).

37.4.1.6 Hemoptysis and Pulmonary Hemorrhage

Hemoptysis is an uncommon event in children and in a majority of cases is quantitatively non-critical and caused by lower respiratory tract infections (LRTI) (Batra and Holinger 2001; Fartoukh et al. 2008; Fabian and Al-Sadoon 1996). Concerns about the occurrence of massive hemorrhage and a long list of differential diagnoses, however, usually are motivation for extensive investigations in order to find the source of bleeding and to establish a causative diagnosis, which can be achieved in about 80 % of cases (Batra and Holinger 2001; Fabian and Al-Sadoon 1996). Bronchoscopy is a valuable tool for hemoptysis work-up, however its limitations. It may be obviated in cases of minor bleeds and known LRTI or before bronchial artery embolization in patients with known causation and localization of hemoptysis (Hsiao et al. 2001). The obvious advantages of bronchoscopy are the direct visualization of lesions in the trachea and proximal bronchi, the opportunity for sampling material, and the possibility of local therapeutic interventions. Aspirated fluid should be cultured for bacteria, mycobacteria, and fungi, supplemented by specific analyses according to the underlying condition. Distal pathologies are not accessible and identification of the feeding bronchus may be impossible if significant amounts of blood spill over into adjacent bronchi. A frothy appearance of the sanguineous bronchial fluid and hemosiderin-laden macrophages in the BAL fluid indicate alveolar provenience of the blood (Maldonado et al. 2009). If no obvious source can be seen, the upper airways should be investigated, as blood loss from the nasal cavity or the epipharynx may leak into the lower airways of intubated children in significant amounts, particularly if swallowing is impaired. It might be necessary to remove an ETT or a tracheostomy

cannula in order to seek friction lesions caused by the tubes. Patients who require ongoing significant ventilatory support during bronchoscopy might best be investigated with rigid bronchoscopy.

37.4.2 Therapeutic Indications

37.4.2.1 Endobronchial Toilet (Assessment of Lobar Collapse)

Lobar and segmental collapse is a common complication in ventilated children and mostly the result of retained secretions. Other causes for atelectasis are airway pathologies, extrinsic airway compression, or misplaced endotracheal tubes. The greatest concern over prolonged lobar collapse is the development of nosocomial pneumonia and increased hypoxemia through shunting. Endoscopic evaluation is indicated if the cause for lobar collapse is unclear. Although bronchoscopy may not be indicated as an initial procedure to remove respiratory tract secretions in ventilated children, it may provide a benefit in cases where less invasive methods prove ineffective in removing secretions and mucous plugs (Bar-Zohar and Sivan 2004; Scolieri et al. 2004). Thick mucus plugs or casts, such as in plastic bronchitis, may require the use of a rigid bronchoscope to be safely and effectively removed. The instillation of rhDNase can be an effective technique to dissolve thick mucus plugs and to reestablish airway patency (Hendriks et al. 2005; Kamin et al. 2006; El Hassan et al. 2001). Bronchoscopy seems a less effective modality in patients who exhibit subsegmental atelectasis or air bronchograms on chest X-rays (Kreider and Lipson 2003). Drawing further conclusions about the best management of lobar atelectasis in ventilated children and even adults is not justified given the lack of scientific studies on this topic (Schindler 2005).

37.4.2.2 Selective Intubation

Selective single-lung ventilation has been used in premature infants and older children with severe unilateral pulmonary hyperinflation preventing adequate ventilation of the contralateral side and/or causing cardiovascular compromise. Lung isolation during mechanical ventilation may also be

beneficial in patients with a bronchopleural fistula or severe, asymmetric lung injury or infection. Techniques for lung isolation include use of a single-lumen ETT advanced into a main stem bronchus (unilaterally or bilaterally), use of a bronchial blocker (including a balloon-tipped catheter or a Univent® tube), and use of a double-lumen ETT (Hammer et al. 1999; Brady et al. 2005). Using these techniques, the healthy lung may be ventilated while the diseased lung is isolated and deflated. In rare circumstances, both lungs are ventilated with different ventilatory modes (Hammer 2004).

Fiber-optic bronchoscopy allows for a quick and nontraumatic selective intubation of either bronchus with a single-lumen ETT tube in even the smallest infant (O'Donovan et al. 1999). Fiber-optic bronchoscopy is obviously most helpful to intubate the left main stem bronchus, since passage in the right lung can often be accomplished by blindly advancing the endotracheal tube beyond the carina. Deflation and isolation of severe unilateral barotrauma for localized hyperinflation, such as interstitial emphysema in premature neonates, often results in absorption of the extra-alveolar air and cardiovascular stabilization within 5–48 h and is commonly maintained for 1.5–5 days (Fig. 37.1) (Campbell et al. 1984; de Vries and Senders 1984; Brooks et al. 1977; Meyer et al. 2002). Selective bronchial intubation is generally unsuccessful in permanently correcting congenital lobar emphysema (Glenski et al. 1986). However, emergency pneumonectomy in neonates and infants due to life-threatening overinflation of one lung may be avoided by selective unilateral intubation of the main stem bronchus of the compressed lung (Holzki and Keller 2003).

Double-lumen tracheal tube may be used in certain rare instances to isolate the two lungs for differential ventilation in the PICU, as well as for the selective delivery of inhaled medications (Almodovar et al. 2000). There are limited options for differential lung ventilation in pediatric patients, because the smallest double-lumen ETT has an outer diameter similar to a 6.0 cuffed ETT. Routine flexible bronchoscopy is recommended to verify tube position after intubation with a double-lumen ETT or a bronchial blocker (Klein et al. 1998). Correct recognition of tracheobronchial

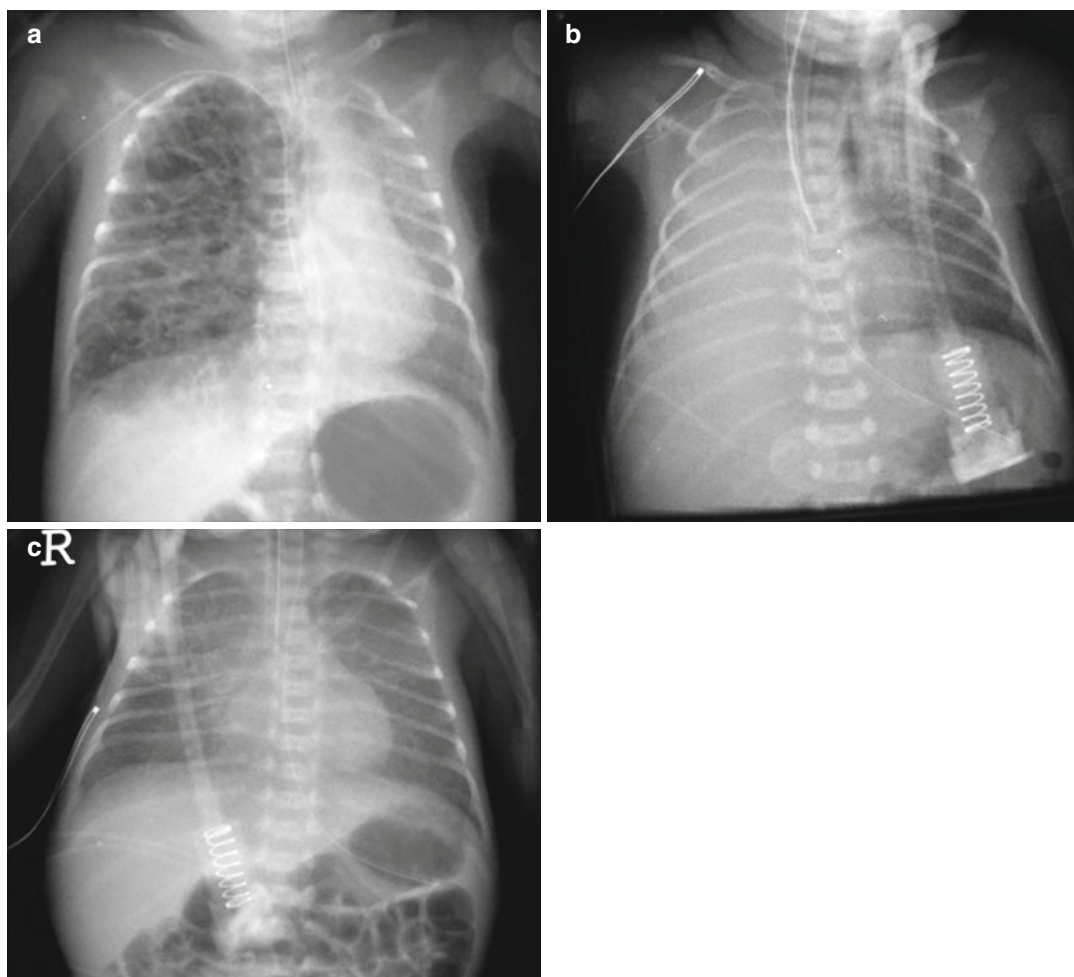


Fig. 37.1 (a) Severe unilateral pulmonary interstitial emphysema (PIE) in a premature ventilated baby causing mediastinal shift and cardiovascular compromise. (b)

Unilateral intubation guided by fiberoptic bronchoscopy. (c) Resolution of the PIE after withdrawing of the endotracheal tube after 36 hrs

anatomy and familiarity with the use of the flexible fiber-optic bronchoscope are essential skills to manage patients with double-lumen tubes or bronchial blockers safely.

37.4.2.3 Whole Lung Lavage

Pulmonary alveolar proteinosis is a rare disease, characterized by excessive intra-alveolar accumulation of surfactant lipids and proteins, and occurs in three clinically distinct forms: congenital, secondary, and acquired (Trapnell et al. 2003). Whole lung lavage has been described as a therapeutic option in selected children with pulmonary alveolar proteinosis. Small children do not allow positioning a double-lumen ETT. In

this situation, lung lavage can be performed by inserting a balloon catheter with a distal opening through an ETT, which is then wedged into one of the main stem bronchi. Endoscopic control of the exact position and tight fit of the balloon with a very thin endoscope enhance the safety of this intervention (Paschen et al. 2005; Nicolai 2001; Mahut et al. 1996; McKenzie et al. 1989). Therapeutic lavages are done with up to 20 mL/kg body weight aliquots of normal saline and continued until the recovered fluid is gradually clearing. Depending of the size of the lung, this may require as much as 1–2 L for small children and up to 8–10 L for adolescents (Ceruti et al. 2007; Paquet and Karsli 2009).

37.4.2.4 Percutaneous Dilatational Tracheostomy

Percutaneous dilatational tracheostomy has become a routine intervention in adult intensive care units since its first description in 1985 by Ciaglia (Veenith et al. 2008; Kluge et al. 2008). The Ciaglia procedure uses a dilator over a guide wire technique and is usually done at the bedside in the intensive care unit under fiber-optic bronchoscopic guidance in the intubated patient. Inadequate training and lack of familiarity with the technique are associated with an increased complication rate. There are also anatomical and medical conditions in which a surgical tracheostomy may be safer. This applies to the pediatric age group, where percutaneous dilatational tracheostomy is rarely undertaken and also controversial (Principi et al. 2008; Scott et al. 1998). Children have a smaller and more compliant trachea than adults leading to a tendency to collapse when pressure is exerted with dilators. Hence, this could lead to a lower success rate, higher incidence of posterior wall injury, and the possibility of invaginated fractured cartilage if the dilatation occurs through and not between the tracheal rings (Bell 1998). Severe tracheal stenosis has been described as sequel of such procedures in children (Scott et al. 1998). None of the commercially available dilatational tracheostomy sets are registered for use in children. Nevertheless, its use in pediatric intensive care has been described in case series, especially in children older than 10 years of age and in adolescents (Toursarkissian et al. 1994). The use of a rigid bronchoscope instead of a fiber-optic scope (through the ETT) may secure ventilation and eliminate tracheal squashing during the procedure in younger children (Fantoni and Ripamonti 2002). It has been suggested that endoscopy should be performed routinely before decannulation in children to detect and treat granulation tissue and other complications of the procedure (Scott et al. 1998).

The translaryngeal approach described by Fantoni et al. may be a safer technique in children below 10 years of age and offers another option to surgical tracheostomy (Zawadzka-Glos et al. 2004; Fantoni and Ripamonti 1997). In this procedure an armored tracheal cannula is pulled out-

wards through the oral cavity, larynx, and trachea without exerting external pressure to the compliant trachea. The procedure is performed under direct endoscopy, via rigid or flexible bronchoscope. This approach offers a high level of intrinsic safety with regard to the compliant trachea of children. Other advantages are the complete absence of loss of blood, minimal local trauma, and a perfect adherence of the stoma to the cannula.

Further research to investigate the role of non-surgical tracheostomy techniques in selected groups of ventilated children is indicated, especially since in a recent survey the vast majority (81 %) of pediatric intensivists do not agree that the risks associated with percutaneous dilatational tracheostomy outweigh the potential benefits (Principi et al. 2008). Nevertheless, formal trials using especially designed equipment and techniques adapted for young children are warranted before routine clinical use of nonsurgical tracheostomies can be safely recommend in this age group.

37.4.2.5 Foreign Body Removal

Foreign body aspiration is a very common indication for bronchoscopy in pediatric practice outside the intensive care environment. Nevertheless, it is not always immediately diagnosed and may be a rare cause for respiratory failure ending in the pediatric intensive care unit (Jhamb et al. 2004). The symptoms can be nonspecific, and the chest radiograph findings are frequently normal or display abnormalities uncharacteristic for foreign body aspiration. Children in respiratory failure with a history suspicious of foreign body aspiration should undergo prompt bronchoscopy regardless of the radiological findings. Foreign body extraction is commonly performed by rigid bronchoscopy.

37.4.2.6 Tracheobronchial Stent Placement

Airway obstruction due to malignant disease is very rare in children and benign causes such as tracheobronchial malacia or postoperative tracheal stenosis are reluctantly treated with tracheal stents, because these hardly represent a permanent solution considering growth and long-term experience with such devices. Nevertheless,

airway stents are used in the management of severe pediatric tracheal, carinal, and bronchial disease. Airway stenting can help to treat tracheomalacia, bronchomalacia, fixed tracheal obstruction, and postoperative tracheal stenosis after tracheal reconstruction. They also offer a therapeutic option in life-threatening inoperable obstruction of the trachea. At present, intraluminal stent therapy should be the last resort to restore airway patency in children, because complications are common. Fiber-optic bronchoscopy may be helpful in intensive care units taking care of ventilated children with tracheobronchial stents to assess complications such as stent migration or the formation of granulation tissue (Nicolai et al. 2001; Jacobs et al. 2000; Fayon et al. 2005; Anton-Pacheco et al. 2008).

37.4.2.7 Hemoptysis and Pulmonary Hemorrhage (For Diagnostic Considerations, See Sect. 4.1.6)

Massive pulmonary hemorrhage is a rare but distressful event putting the patient at risk of asphyxiation, rather than shock from exsanguinations. The crucial and delicate issue is time. If there is no time for imaging or for transferring the patient to the interventional radiology suite for catheter embolization, rigid bronchoscopy should be first choice in smaller children. Rigid bronchoscopy permits efficient simultaneous ventilation, and large-bore suction catheters allow better clearing of the airways than the small aspiration channels of pediatric flexible bronchoscopes (Sidman et al. 2001). Blocking of the feeding main bronchus by means of a balloon catheter inserted via the rigid bronchoscope may establish sufficient gas exchange. As another temporary measure, the non-bleeding bronchus may be intubated selectively with a cuffed tube under fiber-optic guidance. In adolescents, a double-lumen ETT may be an option, but primary misplacement or secondary dislodging of these tubes is common, and, in addition, rough airway manipulation may be hazardous in the multi-traumatized patient (Klein et al. 1998; Dweik and Stoller 1999; Kabon et al. 2001). Selective tamponade of the bleeding bronchus

with a (4Fr) Fogarty catheter inserted via a flexible bronchoscope requires a suction channel of ≥ 2 mm diameter (Jean-Baptiste 2000). With less life-threatening hemoptysis, a vasoconstrictive drug, e.g., 5 mL epinephrine 1:10,000 (Sidman et al. 2001) or ≤ 0.5 mg terlipressin (Tüller et al. 2004), may be applied locally with the flexible bronchoscope. Success has also been reported with systemic and local application of tranexamic acid (500 mg/5 mL), a synthetic antifibrinolytic agent (Solomonov et al. 2009; Graff 2001).

37.5 Summary

Bronchoscopy has become an important diagnostic instrument in pediatric intensive care. Even more vital, though, is its therapeutic role in emergency situations for managing difficult airways or extracting foreign body aspiration. It is in the intensive care specialist's interest to become perfectly familiar with this technique to be able to apply it safely in ventilated patients and critical situations. It is in the patient's interest that the competing institutional faculties performing bronchoscopies come to terms on how to provide sufficient training and maintain expertise required for an around the clock availability of this essential tool in their institution.

Essentials to Remember

- Try not to cause turmoil using a bronchoscope in the ICU:
 - By applying adequate safety requirements
 - By using adequate monitoring and personal assistance
 - By using equipment adequate for age and condition
 - By referring to a colleague with ample expertise in airway endoscopy
- Remember that bronchoscopy may adversely affect hemodynamic stability and increase intracranial pressure of critically ill patients

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Part XIII

Sedation, Analgesia and Neuromuscular Blockade During Mechanical Ventilation

Sedation, Analgesia and Neuromuscular Blockade in the Neonatal ICU

38

Elaine M. Boyle and K.J. Sunny Anand

Educational Aims

- To describe the indications for the use of analgesia, sedation and neuromuscular blockade in the neonatal intensive care unit
- To describe the effects, benefits and risks of commonly used analgesic, sedative and neuromuscular-blocking agents
- To explain methods for the assessment of need for and adequacy of therapy with analgesic, sedative and neuromuscular-blocking agents
- To describe methods for appropriate weaning and discontinuation of therapy

The use of analgesics, sedatives or muscle relaxants for the management of ventilated neonates is common but provides a regular source of controversy in the practice of newborn medicine. Most practitioners have developed personalised approaches, leading to huge variations in clinical practices within the same institution, which are

markedly accentuated across different institutions. One study, for example, found a 28.6-fold variation in opioid administration among nonsurgical neonates treated at 6 NICUs within the same geographical region (Kahn et al. 1998). The goals of such therapy include tolerance of invasive procedures, maintenance of physiological stability, retention of therapeutic devices and prevention of the long-term effects of neonatal pain or stress, but these are often not clearly defined at the bedside. Also, there are significant concerns about the potential effects of analgesics or sedatives on brain development, despite a lack of correlation between animal studies and human data (Anand 2007; Durrmeyer et al. 2010). The current state of the art allows few recommendations for clinical practice, as the evidence supporting specific approaches for the management of mechanically ventilated neonates remains limited in many areas.

38.1 Pain Control

Historically, the issue of pain in the newborn infant was largely overlooked, reflecting commonly held beliefs that neonates were incapable of experiencing or responding to pain. More recently, through meticulous research in animals and humans, this has changed, and it is now recognised that even preterm infants are sufficiently mature to perceive and respond to painful stimuli. In addition, prolonged or repeated pain in the neonatal period has been associated

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with adverse long-term outcomes including altered pain responses, dysregulation of stress responses or poor cognitive outcomes in later life (Taddio et al. 1997; Grunau et al. 1998, 2007). Advances in obstetric and neonatal care have led to the improved survival of large numbers of sick mature and immature infants. However, research focusing on neonatal pain is in its infancy, and many aspects remain incompletely explored, particularly in the preterm infant.

38.1.1 Indications

The majority of neonates admitted for neonatal intensive care will require some form of respiratory support. Mechanical ventilation is reported to be a significant stressor by articulate adults and children (Novaes et al. 1997, 1999; Simini 1999; Gelinis et al. 2004) and has been associated with significant increases in biochemical stress responses that can be reduced by analgesia (Guinsburg et al. 1998). Appropriate analgesia also improves respiratory function, particularly in larger term neonates in whom decreased lung compliance, hypoxaemia and atelectasis appear to be related to pain (Bolivar et al. 1995). In preterm infants, the use of opioids improves synchrony with the ventilator and reduces the duration of oxygen therapy (Dyke et al. 1995).

Whereas adequate analgesia is regarded as essential and routine therapy for adults and older children undergoing mechanical ventilation, this is not the case in neonatal medicine, and the routine use of analgesia remains controversial. Lack of consensus among clinicians relates to differences in interpretation of the balance between risks and benefits associated with the pharmacological and non-pharmacological management of pain.

A number of clinical research studies have sought to clarify the role of routine continuous or intermittent administration of analgesic drugs (Anand et al. 2004; Simons et al. 2005; Dyke et al. 1995; Orsini et al. 1996; Guinsburg et al. 1998; Quinn et al. 1993; Saarenmaa et al. 1999). Many have focused on the preterm population, the largest of these being the NEOPAIN (NEurological

Outcomes and Pre-emptive Analgesia In Preterm ventilated Neonates) Multicenter Trial (Anand et al. 2004), which enrolled 898 infants to receive continuous infusion of morphine or placebo and failed to show any improvement in short-term neurological outcomes with routine analgesia. A Cochrane systematic review on the use of opioids for term and preterm neonates receiving mechanical ventilation found significant heterogeneity between studies, particularly with respect to methods of pain assessment (Bellu et al. 2008). In most studies, opioids were started at the onset of mechanical ventilation, and the measured effects were small and inconsistent. It was not clear whether this was due to variation in measurement or infant responses. The authors concluded that there was insufficient evidence to support the routine use of opioid analgesia in all ventilated neonates but recommended pharmacological intervention in selected populations and clinical situations. Additional studies to determine clearly the efficacy, safety and long-term effects of analgesic therapies in neonates are much needed.

Given the available evidence and whilst awaiting further research and follow-up, the judicious use of pharmacological measures seems reasonable from a clinical and humanitarian perspective, particularly for selected ventilated babies. Valid indications for analgesia are:

1. When infants are expressing the recognised indicators of pain, possibly quantified with a validated scoring method
2. When the presence of pain can be predicted, based on their clinical condition
3. When pain or distress interferes with effective management of ventilation or other vital supports
4. When environmental and non-pharmacological measures have failed to reduce pain responses

38.1.2 Choice of Drug

Non-pharmacological measures including environmental and developmental interventions, such as positioning, swaddling and minimal handling, can be effective in reducing chronic distress in

babies and may reduce the need for drugs in most cases (Golianu et al. 2007; Cignacco et al. 2010; Westrup et al. 2007). Although the evidence for their use in this group is less convincing than for older children and adults, opioids remain the most extensively studied and used analgesic drugs in ventilated neonates; morphine and fentanyl are the most commonly used drugs. Each drug has potentially beneficial and adverse effects, and there is no consensus as to which is optimal. Choice of drug depends to a large extent on the personal preferences, experience and familiarity of clinicians.

38.1.2.1 Morphine

Morphine is the prototypical opioid. It has a slow onset of action and delayed clearance in neonates compared with older children and adults. It can reduce stress responses (Bouwmeester et al. 2001) and postoperative pain responses (Bouwmeester et al. 2003) and has sedative as well as analgesic properties. Continuous infusions of 5–30 µg/kg/h may be used to maintain effective analgesia, whereas intermittent administration may allow periods of inadequate analgesia between doses (Anand et al. 2004; Durrmeyer et al. 2010). Hepatic metabolism of morphine produces the active metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is a more potent analgesic than morphine, whereas M3G appears to have anti-analgesic and stimulatory effects.

38.1.2.2 Fentanyl

Fentanyl is a synthetic opioid, with a more rapid onset of action and shorter duration of action than morphine. Cardiovascular effects are minimal and it reduces pain responses. Continuous infusions of 0.5–2.0 µg/kg/h are usually adequate for analgesic effectiveness. Fentanyl undergoes hepatic metabolism and renal excretion. Development of tolerance occurs commonly following fentanyl analgesia and is discussed in Sect. 38.1.4.

38.1.2.3 Other Drugs

Short courses of nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin and ibuprofen, are used frequently in preterm ventilated neonates for the closure of patent ductus

arteriosus (Herrera et al. 2007; Ohlsson et al. 2008), but not for pain relief. Prolonged use of NSAIDs for analgesia has not been evaluated, and concerns about adverse effects may render this approach inappropriate, particularly in very sick or premature infants.

Acetaminophen or paracetamol is commonly used in older children and has recently become available in an intravenous preparation that is suitable for intermittent administration in ventilated neonates. However, its safety and efficacy have not been fully evaluated in this group (Allegaert et al. 2008; Palmer et al. 2008).

38.1.3 Assessing Adequacy

Assessment of pain in preverbal neonates is always challenging. Although more than 40 clinical tools are now available to facilitate the assessment of acute pain, there is a relative lack of robust and validated tools designed for the assessment of ongoing or “chronic” pain/distress that might accompany mechanical ventilation. To date, there are only three such tools, the EDIN (Echelle Douleur Inconfort Nouveau-Né) (Debillon et al. 2001), the N-PASS (Neonatal Pain, Agitation and Sedation Scale) (Hummel et al. 2008) and the COMFORTneo (van Dijk et al. 2009). All three are multidimensional scores, including physiological indicators as well as facial expressions, the most sensitive indicator of pain. However, physiological indicators lack specificity for pain, and different external methods of securing endotracheal tubes may distort or obscure facial features, which potentially limits their use in ventilated babies. In addition, it is difficult to differentiate between pain and agitation and the effects of analgesia versus sedation, especially in critically ill infants in whom severity of illness may further complicate their assessment.

Research to identify novel methods of detecting and quantifying chronic pain in neonates is ongoing. Investigators continue to build on the knowledge of behavioural responses (Holsti and Grunau 2007; Boyle et al. 2006). It is likely that the application of noninvasive techniques at the cot side, such as near-infrared

spectroscopy, may provide greater insight into more specific pain indicators (Bartocci et al. 2006; Slater et al. 2008).

38.1.4 Drug Weaning

Opioid dependence is a well-documented phenomenon and is recognised in neonates who are exposed to prolonged therapy. Opioid withdrawal (neonatal abstinence syndrome) was first described in relation to infants exposed to prenatal opiates, but the clinical signs seen in infants following discontinuation of therapeutic opioids are similar. These include crying, sleeplessness, hypertonia, seizures, fever, sneezing, loose stools, tremors, sweating and tachypnoea. In infants receiving ECMO support, signs of withdrawal were observed in 57 % of the babies after a relatively short duration of treatment, with rapid weaning as tolerated to allow reintroduction of enteral feeds. A number of scoring tools have been used to monitor withdrawal, mostly based on the Neonatal Abstinence Score (Finnegan et al. 1975), but few of these were designed and validated for ventilated term or preterm babies. Of these, the 12-item Withdrawal Assessment Tool-1 (WAT-1) appears most promising due to its empirical development, ease of use at the patient's bedside and psychometric properties showing high sensitivity (0.87), specificity (0.88) and excellent convergent and construct validity (Franck et al. 2008).

Work confined to the neonatal population is very limited; there are no validated weaning regimens and no prospective studies comparing various weaning protocols (Anand et al. 2010). Studies have suggested weaning by daily dose reduction with some recommending ongoing daily reductions of 5–10 % of the peak dose and others using initial larger reductions of 20–40 % followed by smaller reductions at intervals ranging from 4 to 24 hourly (Cho et al. 2007). Some have used substitution with longer-acting drugs such as methadone to facilitate weaning (Berens et al. 2006), but this approach has not been evaluated systematically in neonates. Newer scoring systems to aid the weaning of analgesic and sedative medication are not yet widely used (Franck

et al. 2008; Ista et al. 2007). Much research is needed to examine the mechanisms underlying opioid tolerance in neonates and the efficacy of novel therapies to prevent opioid tolerance and withdrawal (Anand et al. 2010).

Weaning from opioid therapy will usually be indicated in the recovering or maturing neonate in whom discontinuation of mechanical ventilation is expected. Reduction of the dose of opioid analgesia aims to facilitate extubation whilst minimising the effects of withdrawal. Until further research clarifies optimal strategies, weaning should be combined with environmental measures to provide comfort and tailored to individual babies based on the duration of their therapy and signs of withdrawal phenomena.

38.1.5 Toxicity and Side Effects

In addition to the problems of dependence and withdrawal, a number of other adverse effects occur with the use of opioids. Results from the NEOPAIN trial showed an association between morphine and a significant increase in the duration of ventilation (Bhandari et al. 2005). Hypotension is a well-recognised unwanted effect of opioids, occurring more commonly with morphine than fentanyl. Morphine contributed significantly to hypotension observed in the first 24 h of life in babies in the NEOPAIN trial, particularly in those with pre-existing hypotension and the most immature infants (Anand et al. 2004; Hall et al. 2005). Studies have consistently shown that opioid use is significantly associated with reduced gut motility and an increase in the time taken to establish enteral feeding (Bellu et al. 2008; Menon et al. 2008; Saarenmaa et al. 1999).

Although tolerance can occur with morphine, it is seen more commonly with fentanyl, necessitating increasing doses of the drug over time to maintain effective analgesia. Few studies have been conducted in neonates, but a retrospective review of 37 term infants during extracorporeal membrane oxygenation (ECMO) showed rapid development of tolerance and requirement for high doses by 6 days of treatment

(Arnold et al. 1990). The most worrying adverse effect of fentanyl is life-threatening chest wall rigidity that can occur with rapid intravenous administration of the drug, making ventilation difficult (Fahnenstich et al. 2000).

38.2 Sedation

In some infants, pain relief alone is insufficient to overcome the clinical signs of distress associated with intensive care interventions. Such infants may benefit from sedation to decrease agitation and facilitate ventilation. Published literature addressing sedation in neonates is sparse, and optimal strategies are yet to be defined.

38.2.1 Opioids

Opioids are commonly used for neonates requiring mechanical ventilation, not only for their analgesic but also for their sedative effects. Issues associated with opioid use are discussed in Sect. 38.1 above.

38.2.2 Benzodiazepines

Benzodiazepines can be given intermittently or as continuous infusions to provide sedative, anxiolytic and hypnotic effects, but they have no analgesic effect. Although there is limited evidence to support the use of benzodiazepines, these drugs are extensively used in neonatal intensive care.

38.2.3 Indications

The use of benzodiazepines was introduced empirically into the care of critically ill newborn infants with the intention of reducing stress associated with mechanical ventilation and increasing the effectiveness of ventilation. However, rigorous investigation of the safety and effectiveness of this group of drugs in the neonatal population is still lacking. Challenges in measuring levels of sedation further complicate the use of benzodiazepines.

Since benzodiazepines have most often been used in conjunction with opioid analgesia, it is difficult to study the effects of these drugs in isolation. Midazolam is widely used, but there have been only three high-quality randomised controlled trials in neonates (Jacqz-Aigrain et al. 1994; Anand et al. 1999; Arya and Ramji 2001). A Cochrane systematic review (Ng et al. 2003) including these trials suggested an increase in adverse neurological outcomes occurs with midazolam use, which was supported by data from other non-randomised studies (Bergman et al. 1991; Magny et al. 1994; Ng et al. 2002). The Cochrane review concluded that there were insufficient data to recommend the use of intravenous midazolam as a sedative in neonates undergoing intensive care and raised concerns about its safety. There are currently no indications for the routine use of midazolam for sedation in neonatal intensive care. Indeed, the Cochrane review of opioids for neonates receiving mechanical ventilation also concludes that, if sedation is required, morphine is safer than midazolam (Bellu et al. 2008).

38.2.4 Choice of Drug

Benzodiazepines produce their effect by activating GABA_A-benzodiazepine receptors, which inhibit neuronal activity. Immature GABA_A receptors in the neonate, however, have the opposite effects, increasing nociceptive behaviour and lacking sedative effects (Koch et al. 2008). Metabolism and excretion are delayed in neonates, particularly in the most immature, compared with older individuals, and prolonged sedation can occur. The optimum dose is not known, but most clinicians have used midazolam infusions of 20–60 µg/kg/h to achieve sedation. There is great variability between individuals in response to midazolam; thus dosing should be individualised if the drug is to be used (Hall et al. 2007).

38.2.5 Assessing Adequacy

The need for sedation is variable between patients, with some requiring deep sedation to tolerate

ventilation, whilst others may require only light sedation. It is reasonable to suppose that such variation also exists in preverbal neonates, and this inevitably contributes to difficulties in assessment of adequacy. Since indicators of stress and pain are so similar in neonates, difficulties exist in quantification of pain relief and sedation, and it is a formidable challenge to attempt to separate the two. The N-PASS (Hummel et al. 2008) seeks to combine the assessment of prolonged pain with that of sedation, but validity and reliability have been assessed in a relatively small and heterogeneous group of infants. Another assessment tool, the State Behavioral Scale, was proposed for use in ventilated infants and young children, but this too was tested in a group with widely varying ages from 6 weeks to 6 years (Curley et al. 2006).

There is currently no consensus as to the optimal level of sedation to be achieved in ventilated infants and no well-validated scale to facilitate assessment of sedation. Further work in this area is needed before any recommendations can be made.

38.2.6 Drug Weaning

Discontinuation of benzodiazepines leads to disinhibition of the central nervous system due to reduced efficacy of receptor availability of GABA. Withdrawal is characterised by stimulation of the central nervous system, sympathetic nervous system activation and gastrointestinal disturbance (Birchley 2009). Benzodiazepines are rarely used as sole means of sedation, being most often combined with opioids. The withdrawal syndromes of the two types of drug show considerable overlap and are difficult to separate. Since benzodiazepines are not recommended for routine use in neonates, opioids are most likely to be employed for their sedative effects. Weaning of these drugs has been discussed in Sect. 38.1.4.

38.2.7 Toxicity and Side Effects

Adverse effects of midazolam are most frequently associated with intermittent bolus dosing rather than the use of continuous infusion. It causes

hypotension due to vasodilatation, particularly in infants who already have low blood pressure and, if used in combination with opioids, this effect may be exacerbated (Burtin et al. 1991). Researchers have shown that decreased cerebral blood flow velocity and cerebral blood oxygenation decreases within a short time of administering a bolus of midazolam (van Alfen-van der Velden et al. 2006). Abnormal clinical neurological manifestations that may be related to cerebral hypoperfusion have been observed in a number of studies. These transient effects include hypertonia, myoclonus and abnormal movements (Bergman et al. 1991; Magny et al. 1994).

38.3 Neuromuscular Blockade

Natural breathing efforts in ventilated infants may compromise respiratory and haemodynamic stability, increase oxygen consumption and metabolic demand and potentially cause barotrauma. The potential advantages of pharmacological paralysis lie in the complete elimination of the infant's spontaneous respiratory effort and optimisation of mechanical ventilation. This in turn may decrease the duration of ventilation, reduce air-leak syndromes, dislodgement of monitoring devices or other complications and improve outcomes.

38.3.1 Indications

Asynchrony of breathing in mechanically ventilated newborn infants is a common problem, colloquially referred to as "fighting" the ventilator. This asynchronous breathing is associated with a number of complications, such as pneumothorax and higher intrapulmonary pressures, particularly in larger late preterm or term neonates. In preterm infants, changes in cerebral blood flow can occur that may promote intraventricular haemorrhage (Perlman et al. 1985; Colditz et al. 1989). Paralysis may therefore be indicated in infants who are not breathing in synchrony with the ventilator and are at risk for such complications. A recent Cochrane review (Cools and Offringa 2005) analysed data

from six randomised controlled trials (Bancalari et al. 1980; Greenough et al. 1984; Perlman et al. 1985; Pollitzer et al. 1981; Quinn et al. 1992; Shaw et al. 1993) including 486 preterm infants in total. This review concluded “the routine use of neuromuscular blockade in a selected population of ventilated preterm infants breathing in asynchrony with the ventilator results in a reduction of intraventricular hemorrhage and possibly of pneumothorax”. However, it was not recommended for routine use in all ventilated neonates. Unfortunately, most of these studies predate the routine use of surfactant in preterm infants, which is known to have a major impact on respiratory outcomes, so caution is urged in interpretation of these results and further studies are needed to guide current clinical practice. No data from controlled trials are available for term born infants or for long-term outcomes associated with neuromuscular paralysis.

For neonates recovering postoperatively or requiring transport, neuromuscular blockade may be advantageous for a limited period of time to allow more precise control of ventilation and oxygenation, for example, following cardiac surgery, or to reduce complications that may be caused by excessive body movements.

38.3.2 Choice of Drug

Maturation of neuromuscular transmission continues to occur after birth for the first two postnatal months (Goudsouzian 1980), which can result in variability in response to neuromuscular-blocking drugs.

There are a number of considerations when selecting a neuromuscular-blocking agent although, since these drugs are not used frequently in neonates, familiarity with a particular drug may be a powerful influence. Factors influencing the choice of drug are speed of onset of action and duration of the drug, as well as the length of time for which the need for paralysis is anticipated.

Succinylcholine is the only depolarising agent that is used in neonatal practice. It has a rapid onset but very short duration of action and

therefore cannot be used for prolonged paralysis in ventilated babies. Succinylcholine has a number of side effects including supraventricular tachycardia, pulmonary oedema and prolonged Type II neuromuscular blockade. It is contraindicated in neonates with hyperkalaemia, neuromuscular diseases, birth trauma (or muscle injury), burns, renal failure, pneumothorax, glaucoma, intestinal obstruction, increased intracranial pressure and other conditions. As a substitute to succinylcholine, a number of non-depolarising agents have been developed although none quite have the desired features of an ideal muscle relaxant including rapid onset and favourable side-effect profile. Studies of newer drugs in the preterm neonate are sparse.

All studies included in the systematic review of neuromuscular paralysis in ventilated infants used pancuronium. One of the oldest muscle relaxants, it is a long-acting drug and is most commonly used in neonates. Atracurium has intermediate duration of action. Its advantage lies in its metabolism, which occurs by spontaneous Hoffman degradation at physiological pH and temperature, independent of renal and hepatic processes, making it particularly suitable in multi-organ failure. Onset of action is less than 3 min, and recovery occurs within 30–40 min. Tachyphylaxis can occur with continuous infusion, leading to increased dosing requirements over time. Cisatracurium, the *cis*-*cis* isomer of atracurium, has also been used, but minimal data are available in infants. Vecuronium, another long-acting muscle relaxant, has been compared with cisatracurium in neonates after cardiac surgery (Reich et al. 2004), suggesting that recovery time is prolonged with vecuronium, sometimes exceeding 4 h in one-third of the patients studied. Rocuronium and mivacurium have the fastest onset of action among all non-depolarising agents, thus promoting their use prior to tracheal intubation. However, there are little or no data to guide their use in neonates.

38.3.3 Assessing Adequacy

There are no clinically accepted methods for assessing either whether an infant is breathing in

asynchrony or whether neuromuscular paralysis is adequate. Clinicians using these drugs usually rely on clinical impression of the infant's respiratory status.

Variability presents challenges in predicting the response of individual infants to neuromuscular blockade. Monitoring of adequacy is desirable, both to assess for tachyphylaxis with non-depolarising agents and to avoid drug accumulation and unwanted prolongation of paralysis. Peripheral nerve stimulation may be used to assess the level of neuromuscular blockade, and routine daily discontinuation of the drug can help monitor likely time to recovery. A survey of the UK paediatric intensive care practice suggested 16 % (range 0–60 %) of children receiving neuromuscular blockers would have routine monitoring using a peripheral nerve stimulator (Playfor et al. 2003). Only 38 % of units reported using temporary discontinuation of paralysis to assess neuromuscular recovery (Playfor et al. 2003). Monitoring of neuromuscular blockade is rarely, if ever, performed in neonatal intensive care, mainly because it is painful and the results are unpredictable in neonates. Careful clinical examination should be used to ensure that the desired effect of therapy is achieved whilst avoiding risks of toxicity.

38.3.4 Drug Weaning

When neuromuscular blockade is no longer necessary, drugs are usually discontinued rather than weaned; occasions when incomplete paralysis would be desirable are difficult to identify.

38.3.5 Toxicity and Side Effects

Prolonged immobility associated with pharmacological paralysis has been associated with prolonged weakness and muscle contractures (Sinha and Levene 1984), but, in clinical practice, a more commonly observed effect is significant oedema during paralysis. Whilst this usually subsides rapidly when the baby is again able to move, it can produce challenges in caring for infants and particularly in skin care.

The absence of a blink reflex in paralysed infants places them at risk of eye infection or corneal abrasion, and meticulous eye care is required. Tachycardia and hypertension have been reported with pancuronium (Caball et al. 1985). Rapid injection of atracurium can produce histamine release and hypotension (Martin et al. 1999). Vecuronium, in contrast, has few cardiovascular effects.

Additional disadvantages of using neuromuscular blockade lie in the masking of other conditions. Clinical seizure activity may not be evident, necessitating cerebral function monitoring to assess neurological status. Similarly, infants are unable to display signs of pain. This necessitates the use of analgesic medication alongside paralysis to ensure infants' comfort.

38.4 Important Unknowns

There are many gaps in our knowledge. Pain relief, sedation and neuromuscular blockade are all important aspects of neonatal intensive care, yet many questions remain unanswered about how to optimise treatment with pharmacological agents. Further rigorous scientific exploration of current and new methods for detecting and quantifying pain and sedation is crucial to guide pain management. Efficacy and safety of many of the commonly used drugs remains uncertain, and information about long-term effects of therapy is scant. Many of the newer neuromuscular-blocking agents have simply not been tested in the neonatal population. Further research in all these areas is long overdue and should be addressed as a matter of priority, both from the humanitarian and scientific standpoints.

Essentials to Remember

- Non-pharmacological measures should be used in the management of pain in ventilated infants and may reduce the need for drugs.
- Analgesia, sedation and neuromuscular blockade should be used only if

indicated in selected ventilated infants. Routine use is not recommended.

- Effects of analgesic, sedative and neuromuscular-blocking drugs should be monitored carefully to maximise benefit and minimise adverse effects.

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Sedation, Analgesia and Neuromuscular Blockade in the Paediatric ICU

39

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Educational Goals

An understanding of the scientific basis of sedation and analgesia and their application to clinical practice in paediatric intensive care:

- The importance of individualised dosing regimens
- A review of currently used sedation, analgesia and muscle relaxants
- Assessment of effectiveness of the agents
- Current approaches to drug weaning
- An overview of new horizons in intensive care sedation

39.1 Introduction

Infants and children admitted to the intensive care unit require treatment for their primary disease and maintenance of bodily functions (fluid balance, energy intake, temperature control) to optimise recovery. Additional treatments provide analgesia, reduction of conscious level and, when indicated, muscle relaxation. While these three form the basis of classical anaesthesia in paediatric intensive care, they are used for longer periods, often below the levels required for surgical procedures and with different goals. This brings to the fore specific problems related to the drugs such as altered drug pharmacokinetics and drug responses, tolerance and withdrawal, toxicity associated with long-term use and the need to effectively monitor drug effect against delivery. Sadly, administration of sedation drugs in PICU is often approached in a generic way and as an afterthought with more concentration paid to the primary disease, and this can lead to avoidable morbidity.

Undersedation and oversedation are both harmful. Inadequate sedation is unacceptable in a vulnerable child that may be unable to move or communicate its distress due to the use of muscle relaxants, while the unparalysed child may “fight” the ventilator, leading to ineffective ventilation, accidental extubation or the loss of invasive access or monitors. In intensive care, agitation and inadequate sedation has been correlated with adverse short-term and longer-term outcomes (Tonner et al. 2003; Kehlet and Holte

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2001). In contrast, oversedation delays recovery, promotes tolerance to the drugs and leads to distressing symptoms on withdrawal of the drugs (agitation, seizures, hallucinations, psychosis, fever and tachycardia) (Tobias 2000). Maintaining ideal analgesia while at the same time promoting earlier extubation and PICU discharge can be difficult to achieve: infants have an almost binary state of consciousness (Murray et al. 2004), and a normally active 3-year-old cannot easily be persuaded to remain quiescent for long periods in the intensive care environment using non-pharmacological comforting procedures alone. In the current healthcare environment, there are considerable consumer/parental pressures to ensure that all discomforts whether real or perceived are avoided. Effective analgesia with early mobilisation can be hard to achieve, but recent advances in drug choices, patient monitoring and other therapeutic options offer new prospects for the future. It is imperative to appreciate that good “analgesedation” is a key component of obtaining good outcomes and minimising PICU length of stay, and this requires an understanding of the individual drugs and the pharmacokinetic/pharmacodynamic variations that occur with organ dysfunction and maturity of the child.

Simplistically, analgesic drugs should be given for pain relief, sedative drugs should be given for reduction of conscious level and muscle relaxants used only for specific situations when paralysis is a necessity (e.g. low cardiac output state when it may be necessary to anaesthetise, paralyse and cool a child). There is some crossover in these roles: morphine has sedative properties, ketamine provides analgesia and anaesthesia and even muscle relaxants may have an additive effect on reduction of conscious state through deafferentation (Bonhomme and Hans 2007). These drugs may also have additional properties which may be exploited therapeutically in specific situations, for example, the use of high-dose opioids in the management of pulmonary hypertension.

The key goals of this chapter are to consider the drug options and effects and how combination therapy can be optimised. Other supportive measures will be considered.

39.2 Pain Control

39.2.1 Indications

The requirements for analgesic drugs to control or eliminate pain are a basic human right, but evaluation can be difficult in an infant or a child who may be unable to communicate through immaturity or the constraints of critical care (intubation, paralysis, etc.). Failure to provide adequate analgesia in this setting may have more than the immediate consequences: it is associated with long-term dysregulation of nociceptive mechanisms, which may change behaviours and responses to sensory and pain stimuli (Tonner et al. 2003; Kehlet and Holte 2001; Walker et al. 2009). In contrast, excessive use of opioids also has longer-term consequences. Both human and animal data suggest that early opioid exposure increase subsequent pain sensitivity (Tobias 2000; Murray et al. 2004) and lead to an increased risk of drug abuse in later life.

Analgesic drugs also have additional effects that can be exploited in the care of the critically ill child. Potent opioids such as fentanyl and sufentanil delivered at doses higher than that required simply for analgesia can obtund haemodynamic and adverse hormonal and metabolic responses in the critically ill. The studies by Anand and others demonstrated that high-dose opioids used during surgery were associated with reduced stress response, nitrogen loss, postoperative complications and mortality (Walker et al. 2009; Duncan et al. 2000; Anand et al. 2004). This led to a view that high-dose opioid analgesia, which aims to obtund measured responses to surgery, is a key to good outcome in the high-risk surgical infant (Duncan et al. 2000; Rigby-Jones et al. 2007). However, less is known about the benefits of high-dose opioids in the context of general paediatric intensive care. Certainly, high-dose opioid administration has been shown to be beneficial in the prevention and treatment of specific situations such as hypertensive crisis in the at-risk infant (Guignard et al. 2000) and may benefit patients with a low cardiac output state or those with a critically balanced pulmonary to

systemic shunt, but data is limited outside these specific areas. Furthermore, initial exposure to high-dose opioids is associated with hypotension (Duncan et al. 2000), and the whole issue of benefits versus side effects of opioids in the critical care setting has been highlighted by the results of the “NEOPAIN” study (Anand et al. 2004). This has been dealt with in the previous chapter. The findings have been subject to considerable debate but suggest that in preterm neonates given morphine in a more liberal fashion than the control group, observed comfort was improved at the expense of systemic hypotension. This was associated with increased risk of significant short-term and long-term neurological injury and adverse outcomes. While the care of the newborn neonate is a special case, the inference in PICU is clear: provision of opioids mandates careful management to avoid cardiovascular compromise at whatever dose is provided. Children with severe cardiovascular compromise need careful cardiovascular monitoring and the availability of supportive therapy when first exposed to intense analgesia, although in children with raised pulmonary vascular resistance, high-dose opioids may paradoxically result in a rise in blood pressure as pulmonary resistance drops.

39.2.2 Choice of Drug

Although deep sedation and anaesthesia can obtund the behavioural responses to pain, there are limited groups of drugs that can provide true analgesia. These are summarised in Table 39.1.

39.2.2.1 Opioids

Opioids remain the mainstay of analgesia in paediatric intensive care. Morphine, one of the main active ingredients of opium, was first isolated in the 1800s and is still in use today. Other drugs from this group that are used in PIC include fentanyl, alfentanil and remifentanyl.

Pharmacokinetics of the opioids are age dependent and related to the maturity of hepatic and renal elimination routes. They are also highly influenced by the effect of the primary disease

Table 39.1 Choices of analgesia

Systemic analgesia	Local anaesthesia
<i>Low-dose opioids</i> (in order of increasing potency) Codeine, morphine, fentanyl, alfentanil, remifentanyl	<i>Local anaesthesia</i> Lignocaine, bupivacaine, L-bupivacaine, ropivacaine
<i>High-dose opioids</i>	<i>Routes</i>
<i>NMDA antagonists</i>	Topical:
Ketamine	EMLA, LAT gel, amethocaine
<i>Alpha-2 agonists</i> Clonidine, dexmedetomidine	Infiltration
<i>Nonsteroidal anti-inflammatory drugs</i>	Regional blockade
Diclofenac, ibuprofen, ketorolac	Epidural
<i>Paracetamol</i>	Spinal
	<i>Adjuncts to central blocks</i> Clonidine, opioids

process on organ function, drug compartments and fluid balance (Rigby-Jones et al. 2007; Lynn et al. 1998). For the critically ill child in general, there is a combination of an increase in volumes of distribution but a fall in drug clearance as alluded to earlier in the chapter. As a result, drug requirements are high in the initial phases with significant context-sensitive half-time, but once a true steady state is reached, drug accumulation can occur due to reduced clearance. Care therefore must be taken to provide adequate drug loading early on, but once a steady state is reached, infusion rates need to be adjusted to reflect the reduced clearance, particularly if there are reductions in hepatic or renal function. A guideline to the opioid choices and dose ranges are given in Table 39.2.

Neonates have both pharmacodynamic and pharmacokinetic susceptibility to sedatives and opioids, and this may deter the clinician from providing effective dosing. However, unless effective plasma concentrations of the drug have already been achieved during surgery, initial loading doses of the drug may need to be given in the intensive care unit. In contrast, with older infants and young children, it can be difficult to provide effective analgesia and sedation without

Table 39.2 Opioid analgesia

Drug	Indications	Dose	Elimination	Comments
Fentanyl infusions	Analgesia Intense analgesia/anaesthesia in ventilated patients	1–5 µg/kg/h 5–15 µg/kg/h	Metabolised in the liver	Large bolus doses can cause hypotension Neonates may have long elimination half-lives with delayed recovery
Bolus fentanyl	Control of pulmonary hypertension	10–50 µg/kg		Ventilatory depression
Morphine	Analgesia with sedation Controlled analgesia in the extubated patient	Loading dose: 50–200 µg/kg Infusion: 5–80 µg/kg/h Neonates: lower infusion rates 5–20 µg/kg/h	Hepatic followed by renal excretion of active metabolite (morphine-6-glucuronide)	Delayed recovery in neonates Nausea and vomiting can be a problem in older children Reduced doses may be needed with renal impairment due to accumulation of morphine-6-glucuronide
Oral morphine	Longer-term analgesia once absorption has recovered	200–500 µg/kg 4 hourly		Oral doses need to be larger than IV doses due to reduced bioavailability and first-pass metabolism
Alfentanil	Given by infusion Rapid-offset drug useful for fast-track surgery	Loading dose: 50–100 µg/kg Infusion: 0.5–4 µg/kg/min	Metabolised in the liver. Highly protein bound with a small volume of distribution	Its small volume of distribution and short elimination half-life make its offset very rapid
Remifentanyl	Given by infusion in ventilated patients Intense rapid onset/offset (largely independent of age or duration of infusion)	Analgesia: 0.1–0.4 µg/kg/min Anaesthesia: 0.5–1.5 µg/kg/min	Metabolised rapidly by plasma and tissue cholinesterases	Alternative analgesia is required before the infusion is stopped Not suitable in the extubated spontaneously breathing patient
Codeine Phosphate	Oral medication	Neonate: 0.5–1 mg/kg 4–6 hourly Child up to 12 years: 0.5–1 mg/kg max 240 mg per day Over 12 years: 30–60 mg	Hepatic and renal clearance	Also used for treatment of diarrhoea due to constipating effects Poor activity below 5 years Inactive in approx 10 % patients
Tramadol	Oral medication	Over 12 years 50–100 mg every 4–6 h maximum 400 mg/day	Hepatic and renal clearance	Only in patients over 12 years old Nausea and vomiting, constipation Respiratory depression in large doses

resorting to large drug doses, often in combination with multiple sedative drugs. This reflects increased volumes of distribution and large clearance values that may equal or exceed that of adults, compared to relative pharmacodynamic drug resistance in neonates. It is not until adolescence that responses and handling of the drugs approach that of the adult.

All the opioids are associated with tolerance, resulting in increasing opioid requirements to maintain adequate analgesia/sedation, and this is accelerated by high-dose opioid techniques' "acute tolerance". This effect has been shown to be more pronounced in the shorter acting and more potent opioids such as fentanyl and remifentanyl (Guignard et al. 2000). Neonates undergoing ECMO require five times the initial fentanyl infusion rate by day 6 to achieve the same level of sedation due to a combination of enhanced elimination (Arnold et al. 1991) and pharmacodynamic tolerance (Greeley 1998).

Once the alimentary route is effective, there is some evidence that oral opioid administration results in reduced longer-term tolerance (Nestler 2001; Eisch et al. 2000; Pu et al. 2002). Certainly, the use of enteral drug administration reduces infection risk associated with long-term intravenous access and line manipulations (Pronovost et al. 2006) and should be used in preference where possible. Morphine undergoes considerable first-pass metabolism through the liver if absorbed through the alimentary system, and therefore, the dose requirements are considerably greater than by intravenous routes with total daily doses needing to be increased by a factor of five to ten in order to achieve the same level of analgesia compared to the intravenous route.

39.2.2.1.1 Morphine

Morphine has a lower opioid receptor affinity and is more water soluble compared to drugs such as fentanyl. These properties confer relatively low potency and slower onset (10–15 min to maximal effect) due to the time required for the drug to reach an adequate effector site concentration. This also explains the long duration of effect and relatively slow clinical offset with a single dose lasting several hours. This can be

used as an advantage in transition periods for a patient such as in the immediate postoperative phase. A loading dose of 100–200 $\mu\text{g}/\text{kg}$ (or more in the ventilated morphine-naïve patient) followed by an infusion with a rate of 10–80 $\mu\text{g}/\text{kg}/\text{h}$ will provide a reliable level of analgesia for the majority.

Early drug dosing may be needed in the postoperative patient to achieve effective drug concentrations, while infusion rates may need to be moderated with time to reflect the increased volumes of distribution and any reduced hepatic and renal clearance. Reduced renal function regardless of cause will significantly increase the effective half-life of morphine in a patient. This is due to the accumulation of the active metabolite of morphine, morphine-6-glucuronide, in these patients. Conversely all patients have the potential for tolerance to opioids requiring increased doses to achieve the same level of sedation or analgesia.

Intravenous morphine infusions can be adjusted to allow patients to self-ventilate. Adequate regular monitoring using appropriate behavioural scoring such as the COMFORT score (Ambuel et al. 1992; van Dijk et al. 2000) will allow dose adjustment to prevent excessive sedation and respiratory depression. Nausea and vomiting are more usually associated with older children, particularly females, but can usually be controlled with antiemetics and should not prevent the use of adequate analgesia.

Patient-controlled analgesia with morphine can be a useful tool in the extubated child that is able to understand the principle (usually by the age of 5 or 6 years). The usual technique is to have a low background infusion of 5 $\text{mcg}/\text{kg}/\text{h}$ combined with a demand dose of 20 mcg/kg with a lockout time of 5 min (Doyle et al. 1993). This approach leads to analgesia better matched to pain and reduced side effects. For the younger age group, this principle can be applied, and nurse-controlled analgesia has been used successfully using a higher background infusion and a smaller bolus dose. As discussed above, oral morphine should replace intravenous morphine if and when required, provided the alimentary system is functional.

39.2.2.1.2 Fentanyl

Fentanyl is a potent opioid with a faster onset and offset than morphine due to its high receptor affinity and increased fat solubility allowing rapid delivery to the receptor sites. Initial offset with the drug is primarily by continued uptake into the peripheral stores, making it a short-acting drug for single-dose or short-term infusion. However, after 12 h when peripheral stores are largely saturated, the drug has a slow offset (terminal half-life of 3 h in the older child but up to 17 or more hours in the preterm neonate (Katz and Kelly 1993; Collins et al. 1985)) which can then delay recovery if the effects have not been monitored with behavioural scoring or regular drug “holidays”. Infusion rates of 1–5 µg/kg/h are sufficient to provide analgesia. For sick infants where it is being used to maintain anaesthesia, reduce metabolic demand and provide haemodynamic stability, rates of 10–20 µg/kg/h can be used. These higher doses provide blunting of haemodynamic and pulmonary responses to procedures such as endotracheal suctioning and physiotherapy – useful in an unstable patient.

In neonates, high-dose fentanyl alone is considered sufficient to provide complete anaesthesia and sedation. However, infants and children require the addition of hypnotic drugs such as a benzodiazepine, chloral hydrate or clonidine to ensure adequate sedation as well as analgesia.

39.2.2.1.3 Alfentanil

Alfentanil is an opiate that is highly protein bound which results in a small volume of distribution. The result of this is a much shorter elimination half-life than fentanyl with less potential for accumulation (Bower and Hull 1982). Alfentanil is metabolised in the liver to inactive compounds. It is less potent than fentanyl, but its rapid onset and offset makes it a useful drug both in the operating theatre and intensive care unit. As with morphine and fentanyl, the pharmacokinetics are highly age dependant, and the younger-age child has a shorter elimination half-life than adults (Goresky et al. 1987; Meistelman et al. 1987), while the neonate has prolonged elimination (Davis et al. 1989).

39.2.2.1.4 Remifentanyl

This drug is the exception to the opioid class as it is metabolised by plasma and tissue cholinesterases and therefore does not rely on hepatic and renal function. It has a very short half-life of 3–6 min after a single injection and is relatively age independent unlike the other drugs in the group (Ross et al. 2001). Due to this rapid and efficient way of clearing the drug, there is a predictable offset of drug action even in infusions and peripheral accumulation does not occur. However, in common with high-efficacy rapid-offset drugs, it leads rapidly to acute tolerance. While this is a controllable effect for use in the operating theatre or for procedural pain in PICU (Guignard et al. 2000), it precludes its use in PICU as a longer-term analgesic that can be used over days (Vinik and Kissin 1998).

Remifentanyl provides intense opioid analgesia with limited sedative effects. Analgesia is initially provided by doses of 0.1–0.4 µg/kg/min, but for surgical procedures, doses in the order of 1 µg/kg/min are needed in order to completely obtund stress responses (Weale et al. 2004). Due to the potency of the drug, it is difficult to use in a self-ventilating child as with other high-efficacy opioids chest wall rigidity can occur on initial exposure to the drug. This can result in significant respiratory impairment and should be watched out for in the unparalysed ventilated neonate. Bradycardia and hypotension have been reported in neonates on initial exposure to the drug (Weale et al. 2004).

Adult studies suggest that large intraoperative doses of remifentanyl are associated with increased postoperative morphine requirements (Guignard et al. 2000). This means loading with longer-acting opiates is necessary prior to stopping a remifentanyl infusion. The major barriers to further investigation of this drug in clinical practice are its high cost and drug tolerance.

One study looking at fast-track paediatric cardiology patients found remifentanyl was no better than fentanyl in terms of recovery and was associated with a significant (30 %) reduction in heart rate compared to fentanyl (Friesen et al. 2003). Remifentanyl potentially has use via the intranasal route for procedures in PICU. Given as a

single dose intranasally, it provides an excellent pharmacokinetic profile providing increased analgesia for 15 min. This approach avoids fluctuant levels and the attendant side effects of single-dose intravenous or infusion administration of remifentanyl. Verghese et al. have reported this technique for intubation during inhalational anaesthesia with 5 % sevoflurane after a single dose of 4 µg/kg of remifentanyl (Verghese et al. 2008). This exciting new approach would allow modulation of analgesia for physiotherapy, tube change, etc., without having to change existing background infusions of sedation and analgesia or break into the intravenous circuit to give additional bolus doses.

39.2.2.1.5 Codeine Phosphate

Codeine is a simple analgesic that can be administered orally, rectally or intramuscularly. It should not be used intravenously due to the risks of profound hypotension and grand mal seizures. It is commonly used for postoperative analgesia in the paediatric setting for moderate pain, having a place on the World Health Organisation's analgesia ladder. It is most commonly used in conjunction with paracetamol and can in addition be used with nonsteroidal anti-inflammatory drugs (NSAIDs).

Codeine has a low affinity for opioid receptors; 10 % of the drug is metabolised to morphine. There is genetic variability in the amount of morphine metabolised by the cytochrome P-450 enzyme CYP2D6, so patients experience differing analgesic effects (Sasada 2003). An estimated 7–10 % of Caucasians have low levels of the enzyme resulting in poor metabolism and therefore lower levels of active metabolites and reduced analgesic benefits (Tremlett et al. 2010). Conversely some individuals show enzyme duplication and become ultrarapid metabolisers, producing abnormally high levels of morphine and therefore being at greater risk of respiratory depression (Tremlett et al. 2010). Approximately 50 % of the drug undergoes first-pass metabolism following rapid oral absorption. Peak plasma levels occur after an hour in adults with varying rates of clearance in the paediatric population (Tremlett et al. 2010).

The most common side effect of codeine is slowed gut motility that can lead to constipation but has been used as a treatment (Sasada 2003). Some patients experience respiratory depression following codeine administration. The primary mode of metabolism is within the liver, and therefore, caution with dosage needs to be considered in those with hepatic impairment (Sasada 2003). The recognised problem of respiratory depression has resulted in codeine being withdrawn from use both in neonates and breastfeeding mothers.

While there are many theoretical reasons why codeine should no longer be used, it is still prescribed both within and outside the PICU (Tremlett et al. 2010). Familiarity and well-recognised dosing regimens convey an advantage as well as the availability of oral preparations. It has a limited role in the PICU setting as it is generally agreed that codeine is not a substitute for the more reliable and potent analgesic properties of morphine (Tremlett et al. 2010). It is the author's view that oral morphine should be started in preference to codeine where possible.

39.2.2.1.6 Tramadol

Tramadol is a synthetic opioid used in the management of moderate to severe pain. It can be administered orally, intravenously or intramuscularly. The dose for children is 1–2 mg/kg every 4–6 h (Sasada 2003). Eighty five percent is metabolised by the liver; 90 % of the dose is excreted in the urine. Hepatic or renal failure is a contraindication to its use (Sasada 2003). In the UK, tramadol is not licensed for use in children less than 12 years of age.

One major disadvantage of tramadol in paediatrics is the high incidence of nausea in children. As with codeine, the active metabolite is formed via the CYP2D6 enzyme system resulting in a varied analgesic effect depending on the patient's underlying genetics.

39.2.2.2 Non-opioid Analgesics

There are a variety of drugs within this group, the most common of which are discussed below. Table 39.3 summarises this group including doses and the most clinically relevant side effects.

Table 39.3 Non-opioid analgesia

Drug	Indications	Dose	Comments
Paracetamol	Hyperthermia Co-analgesia with opioids	0–3 months loading dose: oral 20 mg/kg, rectal 30 mg/kg Maintenance 15 mg/kg/dose Maximum daily dose (see Table 39.4)	Significant but low analgesic potency Reduced doses may be needed in the critically ill fluid-restricted child to avoid hepatic dysfunction and toxicity
Diclofenac ^a	Opioid-sparing analgesia Not used under 1 year or in children with significant asthma	1 mg/kg/dose or rectal maximal daily dose 3 mg/kg/day	Has effects on gastric mucosa and platelet function Can be nephrotoxic
Ibuprofen ^a	Not used under 3 months or in children with significant asthma	10 mg/kg/dose oral or rectal maximal daily dose 40 mg/kg/day	As above
Ketamine	Alternative intravenous analgesia to opioids (NMDA receptor antagonist)	IV infusion 10–45 µg/kg/min	Can be used in spontaneously breathing children. Associated with dysphoria when used as a sole agent. May provide useful bronchodilation
Clonidine	Less analgesic potency than morphine but can be used as co-analgesia (orally), for longer-term sedation or for withdrawal from opioids (α-2-agonist)	Intravenous: 0.5–3.0 µg/kg/h Oral: 2–5 µg/kg 4 hourly	Can cause hypotension and bradycardia Rebound hypertension has been described in adults

^aThese drugs are used extensively outside their product licence but within recommended guidelines from the Royal College of Paediatrics and Child Health (1997)

39.2.2.2.1 α-2 Adrenoceptor Agonists

39.2.2.2.1.1 Clonidine

Clonidine is an α-2 receptor agonist that has a predominantly central action within the central nervous system to modify sympathetic outflow and alter pain transmission and perception. It has multiple actions and has been used as a nasal decongestant and antihypertensive agent in the past, but in intensive care, it has become of interest as an analgesic and a sedative agent. The drug is fat soluble with high bioavailability (>90 %), making it useful by both intravenous and oral routes. Intravenous doses of 2 µg/kg/h have been used in combination with low-dose midazolam to provide effective postoperative analgesia in paediatric cardiac patients without significant effects on heart rate, arterial blood pressure or cardiac index (Ambrose et al. 2000). It can produce significant hypotension and bradycardia in the adult population in intensive care, and this has been used clinically as a biofeedback loop to regulate infusion rate. Low-dose clonidine [1 µg/kg/h] can give a significant opioid-sparing effect with

subsequent improvement in ventilatory function and conscious level (Lyons et al. 1996).

From adult studies, it is suggested that the use of α-2 agonists is associated with a noticeable lack of drug tolerance and withdrawal (Mirski et al. 1995). In order to reduce opiate requirements postoperatively, some units load patients with clonidine at a dose of 5 µg/kg followed by maintenance doses of 2–4 µg/kg every 4 h. Similar doses are used in children that have been ventilated for prolonged periods who have become tolerant of opiates. This approach has been adapted from the use of oral clonidine in neonatal abstinence syndrome, although a Cochrane Review found insufficient randomised trial evidence to support this practice (Hoder et al. 1984). The therapeutic ratio for clonidine in children appears to be high, and single oral doses of up to 10 µg/kg have been tolerated without apnoea, bradycardia or hypotension (Fiser et al. 1990).

Although the classical withdrawal symptoms seen with drugs such as midazolam do not occur with clonidine, some concerns still remain about

rebound hypertension and agitation, but as yet there are not enough cumulative or prospective data with which to answer these questions.

39.2.2.2.1.2 Dexmedetomidine

As with clonidine, dexmedetomidine's main actions are sedation, anxiolysis and analgesia. It has a purer alpha-2 agonist effect with less alpha-one receptor action (vasoconstriction) and is undergoing evaluation within the United States. The drug is delivered intravenously: dosages involve an initial load at 1 µg/kg for 10 min before reducing the infusion to 0.2–0.7 µg/kg/h. It is only advised for short-term use; infusions are usually stopped within 24 h. The drug is 94 % protein bound with extensive hepatic clearance. The main side effects, as with clonidine, are hypotension and bradycardia (Sasada 2003).

39.2.2.2.2 Non-competitive NMDA Receptor Antagonist

39.2.2.2.2.1 Ketamine

Ketamine is an anaesthetic agent that can provide analgesia and unconsciousness. When given by continuous infusion, it can be used for perioperative pain (Vardi et al. 2002; Green et al. 2001), for procedural pain (Vardi et al. 2002; Green et al. 2001) and as an alternative analgesic to opioids. It usually maintains blood pressure and heart rate after administration due to its indirect sympathomimetic effects despite a limited negative effect on cardiac performance, and this has made it a popular agent for induction of anaesthesia in the child with critical cardiac performance (e.g. cardiomyopathy). Ketamine is associated with hallucinogenic properties and dysphoria that can be offset by combining it with a benzodiazepine.

Ketamine is often selected as an alternative to opioids for analgesia/sedation in the ventilated child with life-threatening bronchospasm, due to its associated bronchodilatory properties. There are limited publications that describe the successful use of ketamine in asthma, but this has never been tested in a large-scale prospective comparative trial (Nehama et al. 1996; Mannix and Bachur 2007). The place of ketamine as an analgesic infusion in PICU remains limited, but it has proved a valuable alternative to opioids in

schemes that allow for cyclical rotation of sedative/analgesic combinations (See Fig. 39.1). Doses up to 2.7 mg/kg/h have been described (Nehama et al. 1996; Hartvig et al. 1993; Tobias et al. 1990; Rock et al. 1986).

39.2.2.2.3 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs can be given in combination with opioids and paracetamol as part of a balanced analgesic regimen to reduce the opioid requirements and their attendant side effects (Mather and Peutrell 1995; Issioui et al. 2002). However, their side effects, including gastrointestinal irritation, prolonged bleeding time due to suppressed platelet function, bronchospasm and renal impairment. Their use therefore needs to be considered with care in the individual PICU patient. The majority of drugs in this class are not licensed for use in children. The most commonly used are ibuprofen (only given over the age of 3 months) and in the older child diclofenac.

39.2.2.2.4 Paracetamol

In isolation paracetamol has limited analgesic potency, but using adequate loading and maintenance regimens can optimise its effectiveness. Children over 3 months of age can be given loading doses of 20 mg/kg orally or 40 mg/kg rectally, followed by regular doses of up to 15 mg/kg every 4 h to provide effective plasma concentrations of the drug (Anderson et al. 2002). The maximum daily oral dosage of the drug in children is 90 mg/kg/day. However, it is generally accepted that in patients who are fluid restricted with reduced cardiac output, dosages should be reduced as hepatic impairment and liver failure can develop when a dose of 90 mg/kg/day is continued in a sick child over several days (Morton and Arana 1999). In neonates, the maximum daily dose is reduced further to 60 mg/kg/day and lower still in preterm infants (Arana et al. 2001). Rectal preparations have reduced and more variable bioavailability than the oral route, and intravenous route may be preferable if the oral route is not available. The duration of use of paracetamol varies with age and can be seen in Table 39.4 (Arana et al. 2001).

Table 39.4 Maximum dose ranges of paracetamol (Arana et al. 2001)

Age of patient	Maximum daily dose (mg/kg/day)	Maximum duration of treatment (h)
Preterm 28–32 weeks	35	48
Preterm 32–36 weeks	60	48
0–3 months	60	48
>3 months	90	72

Paracetamol is frequently used in combination with nonsteroidal anti-inflammatory drugs for pain relief (Morton and Arana 1999). The drug takes up to 90 min to achieve maximal pain relief when given orally and up to 45 min when given intravenously (Moller et al. 2005).

39.2.2.2.5 Local Analgesia Techniques

Afferent pain conduction can be eliminated with effective local anaesthesia applied to the appropriate area with minimal side effects. These can provide an important adjunct to any analgesia or sedation regimen to reduce the drug requirements for background medication or procedural pain. These can be given by a wide variety of routes including topically, infiltration, peripheral nerve blocks or central continuous blocks (epidural or spinal).

Topical anaesthesia is used regularly on the general paediatric wards and in the emergency department. The use of these agents in PICU is often ignored except in non-intubated patients. Procedures seemingly minor such as venous cannulation can be incredibly distressing to the sedated child, often resulting in an increase in baseline rates of sedative infusions. If agents such as Ametop and EMLA are applied in advance of an anticipated procedure, as a routine, the use of intravenous analgesia and sedation can be minimised. Newer, faster-acting agents are now available. Included in this group is lidocaine-adrenaline-tetracaine gel (LAT gel), which is effective for use in as little as 10 min (Ernst et al. 1997; Chipont Benabent et al. 2001). This agent is finding increasing favour in the emergency department for wound suturing, with good effect. It has been suggested that its use should be

extended to other areas, such as PICU, due to its rapid onset of action and excellent analgesic effects. Care does need to be given to its site of use due to the adrenaline component.

Regional anaesthesia remains under utilised in PICU. It can facilitate early extubation and rapid mobilisation following surgery or allow lower levels of systemic analgesia and sedation thereby reducing side effects (Scott et al. 2001; Staats and Panchal 1997; Loick et al. 1999). Included in the realms of regional anaesthesia are intravertebral nerve blocks. These can be applied directly to the nerves by surgeons in theatres following thoracotomies and if necessary repeated in PICU or continued via a catheter. Epidural and spinal catheter techniques for major postoperative chest, abdominal and pelvic surgery have been compared to opioid techniques and can reduce pain, stress response and side effects in comparison to opioids in the short term (Wolf et al. 1998; Humphreys et al. 2005).

39.3 Sedation

39.3.1 Indications

Sedation is a broad term when used in the context of PICU. It comprises many features that may include:

1. Unconsciousness (virtual anaesthesia) or reduction in conscious level
2. Reduced awareness
3. Loss of explicit and implicit memory
4. Compliance with the need to lie in a confined space attached to monitors and invasive lines

The ideal sedative should have a rapid onset, easy administration, predictable duration of action, few side effects and a rapid recovery.

Sedation needs may be low-dose long-term administration, but in addition, the degree of sedation may need to be increased to allow potentially distressing procedures such as physiotherapy, radiological scanning or minor surgical procedures to take place.

Different drugs fulfil these roles to different extents. For example, benzodiazepines provide anterograde amnesia with reduced or complete

unconsciousness at different doses, while phenothiazines and butyrophenones (chlorpromazine and haloperidol) used as major tranquillising drugs in schizophrenia have psychotropic properties that render the patient disinterested in activity. In addition, some of the analgesic drugs described above have dual effects on the reduction of pain and consciousness: ketamine provides analgesia and a dissociative anaesthesia/sedation, clonidine produces analgesia and a calmed relaxed state and morphine has additional sedative properties. Therefore, selection of a sedative regimen needs to be individualised rather than generic.

Neonates are a special group in that morphine alone can often provide enough analgesia and sedation so that a second sedative agent is not required. However, outside this period, almost always an analgesic and a sedative drug are necessary. In the special case where a child needs to receive muscle relaxants, the need for a sedative drug given at adequate dose becomes mandatory to prevent awareness.

In the past, patients in adult intensive care have been given an opioid in combination with a low dose of an anaesthetic agent to ensure pain relief, haemodynamic stability and tolerance to the constraints of ITU. The potentially lethal side effects of anaesthetic drugs over days have only emerged after reviews of death rates and analysis of recurring adverse events. These have included immunomodulation by barbiturates (Galley et al. 2000; Sanders et al. 2009), adrenocortical suppression by etomidate (Fraser et al. 1984) and more recently, mitochondrial dysfunction with propofol in both adults as well as children (Vasile et al. 2003).

Where possible sedation via the enteral route is beneficial. When a patient is able to tolerate feeds and absorb medications via this route, it enables sedation to be given regularly without the need for an infusion and the complications associated with the intravenous route. Many useful sedation agents are well absorbed and tolerated via the enteral route including benzodiazepines, clonidine and chloral hydrate. An additional advantage to oral sedation is it can be weaned gradually and continued following discharge from intensive care if necessary.

39.3.2 Choice of Drug

Table 39.5 summarises the major drugs in this section that are outlined in detail below:

39.3.2.1 Benzodiazepines

39.3.2.1.1 Midazolam

Currently, midazolam is the most common sedative agent in use in PICU (Jenkins et al. 2007). Acutely it can provide effective conscious sedation and amnesia, but used over time, it is a drug associated with major side effects resulting in significant morbidity. Benzodiazepines are associated with tolerance resulting in escalating doses and eventual withdrawal when they are stopped, which are features of all the commonly used sedative agents (Mirski et al. 1995). However, this has been especially noted with midazolam, with data reporting an incidence as high as 35 % with this drug (Fonsmark et al. 1999; Hughes et al. 1994). The duration of symptoms of withdrawal has been found to be as long as 1 week in some patients and can raise concerns about neurological injury while the symptoms continue. Limiting the dose of midazolam to 100 mcg/kg/h can reduce the risks of tolerance and withdrawal, but recent data demonstrated that there was no difference in the incidence of these side effects when the drug was stopped abruptly rather than weaned off over days (Jenkins et al. 2007). It has been shown that any of the commonly used sedative agents in PICU can produce tolerance, physical dependency and withdrawal after prolonged use (Tobias 2000). Midazolam has the advantage of being reversed by flumazenil if necessary.

39.3.2.1.2 Diazepam

Diazepam possesses both anxiolytic and amnesic properties. It can be painful if given intravenously but can also be given orally and rectally. It has a rapid predictable onset and as with midazolam can be reversed with flumazenil (Pershad et al. 1999). Diazepam has some mild muscle relaxation and anticonvulsant properties. It is relatively lipid soluble and water insoluble, and when taken orally, its availability is about 100 %. The sedative level of diazepam is attained some 30 min after oral administration, with the deepest

Table 39.5 Sedative drugs

Drug	Benefits	Dose	Comments
<i>Benzodiazepines</i>			
Midazolam	Provide amnesic benefit in addition to sedation	Infusion max dose of 200 µg/kg/h Intranasal midazolam 0.1 mg/kg/nostril	High risk of withdrawal with prolonged or high-dose (>100 µg/kg/h) use Helps control seizures
Lorazepam	Oral drug useful in midazolam withdrawal	Oral: 0.02–0.06 mg/kg IV: 0.05–0.2 mg/kg, then 0.01–0.1 mg/kg/h	
Diazepam	Rectal for status epilepticus	Rectal doses: Neonate: max 2.5 mg 1 month–2 years: 5 mg 2–12 years: 5–10 mg 12–18 years: 10 mg	Risk of respiratory depression – particularly with repeated doses
<i>Propofol</i>	Short-term action – rapid wake up	Infusion: Max 4 mg/kg/h Titrate to effect Check for rising lactate or acidosis, limit infusion duration	Hypotension Risk of propofol infusion syndrome Lipid load with infusion Contraindicated by FDA
<i>Phenothiazines</i> (chlorpromazine hydrochloride)	Dissociated sedation	Oral or PR: 0.5–2 mg/kg IV: 0.25–1 mg/kg	Risk of extrapyramidal side effects
<i>Butyrophenones</i> (Haloperidol)	Dissociated sedation	Infusion: 1 month–12 years 25–85 µg/kg per day 12–18 years 1.5–5 mg per day	Risk of extrapyramidal side effects
<i>Clonidine</i>	Helpful with withdrawal Analgesic properties with an opiate-sparing effect	Intravenous: 0.5–3.0 µg/kg/h Oral: 2–5 µg/kg 4 hourly	Can cause hypotension and bradycardia Rebound hypertension has been described in adults
<i>Volatile agents</i>	Rapid clearance for quick wake up	Dose titrated to effect Depends on delivery system and gas flows	Can help with bronchospasm and seizures Requires vapouriser and scavenger systems
<i>Chloral hydrate</i>	Well tolerated	25–50 mg/kg oral or per rectum 4–6 hourly	Delayed clearance in neonates – be wary with regular dosing

sedative effects occurring after 60–90 min. In neonates, the volume of distribution is increased, and patients with hepatorenal function impairment will have reduced clearance rates of the drug; therefore, care needs to be given with the dosing in PICU due to the potential for the sedative effects of diazepam to be prolonged by a build-up of active metabolites.

39.3.2.1.3 Lorazepam

Lorazepam is a potent long-acting agent that is a useful drug in PICU, particularly in long-term ventilated patients on oral sedation therapies.

Peak plasma concentration of lorazepam is reached within 3 h of ingestion with a slow offset

(Greenblatt et al. 1979). Patients experiencing symptoms of withdrawal following cessation of intravenous administration of midazolam for a prolonged period can also benefit from oral lorazepam. The acute withdrawal symptoms can be counteracted with the lorazepam, and the dose gradually reduced as the patient recovers. As the drug is well absorbed and tolerated via the oral route, the complications of needing ongoing intravenous access are avoided.

39.3.2.2 Propofol

Propofol was widely used in PICU but is contraindicated by both US and UK regulatory authorities due to life-threatening complications

including metabolic acidosis, rhabdomyolysis and cardiac and renal failure. This syndrome termed propofol infusion syndrome (PIS) (Parke et al. 1992; Bray 1998; Hanna and Ramundo 1998; Cray et al. 1998; Wolf et al. 2001; Mehta et al. 1999) is related to suppression of fat metabolism at a mitochondrial level while continuing to deliver a fat load contained in the propofol emulsion. However, despite the concerns, it continues to be used in specific cases for short-term use at low dose (<4 mg/kg/h). Patients should be closely monitored for rising lactate, acidosis, reduced urine output or dysrhythmias. Haemofiltration to remove the lipid and propofol and provision of adequate carbohydrate intake to suppress further beta oxidation has been recommended as an acute treatment for PIS (Wolf and Potter 2004).

When used as a short-term anaesthetic agent, it can initially cause profound hypotension on first exposure. This brings with it a particular risk for those patients who have cardiovascular compromise secondary to sepsis or underlying cardiac defect. This group are recognised to decompensate when given propofol and potentially spiral into cardiac arrest. While low-dose propofol provides excellent sedation for procedures, it needs to be used with caution as there is a fine line between sedation, anaesthesia and loss of airway control.

39.3.2.3 Chloral Hydrate

Chloral hydrate is a widely used sedative hypnotic. It is commonly used as an adjunct in neonatal and paediatric intensive care. Doses of 25–50 mg/kg can be given either orally or rectally. It is rapidly absorbed from the GI tract and converted to the active metabolite trichloroethanol (TCE). In neonates the parent drug also contributes to the sedation and hypnotic action. The half-life of TCE is 8–12h but is estimated to be three to four times longer in neonates and infants (Pershad et al. 1999). For this reason neonatal doses may need to be revised, particularly with multidose regimens.

Chloral hydrate is a CNS depressant which at therapeutic doses has only mild influence on blood pressure and respirations with no impairment on airway protection reflexes giving it a

good safety profile with the correct dosing range. In overdose the majority of adverse effects occur via the cardiovascular system with a spectrum of arrhythmias that can be fatal. It has a wide safety margin, being detoxified by the liver and eliminated by the kidneys; therefore, hepatorenal disease will affect drug clearance.

Drug interactions are recognised with chloral hydrate exhibiting synergistic effects when given in combination with other sedative drugs. In combination with warfarin, there can be an unpredictable reaction with potential hypoprothrombinaemia due to competition for protein binding. By the same mechanism furosemide in combination with chloral hydrate can lead to vasomotor instability (Pershad et al. 1999).

The action of chloral hydrate is not reversible. It has a relatively long half-life, meaning an extended period of observation may be necessary. Residual motor impairment and lethargy may persist for up to a day following dosing. In chronic overdose dependency syndromes have been described with a withdrawal state including seizures and psychosis.

39.3.2.4 Phenothiazines

This group include a spectrum of drugs that exhibit anticholinergic, 5-HT antagonist and dopamine agonist effects to varying degrees. Clinically this is seen as primarily sedative and anxiolytic effects with a long list of potential side effects. These include extrapyramidal side effects together with the rare neuroleptic malignant syndrome which has a mortality of >10 % (Sasada 2003). Other well-recognised adverse effects in this group of drugs are ECG changes that include a prolonged QT interval.

Some of the advantageous side effects include their action as an antisialagogue and an antiemetic. They are useful adjuncts to pharmacological management on PICU due their ability to allow a patient to be awake yet not concerned about their surroundings with minimal anxiety and a good level of cooperation. The drugs within the group are outlined below with chlorpromazine having more dopaminergic sedating effects at one end of the spectrum and promethazine having primarily anticholinergic effects.

39.3.2.4.1 Chlorpromazine

Outside the PICU, this phenothiazine is primarily used in the treatment of schizophrenia. It can be given orally, intramuscularly or intravenously (by bolus or infusion). It can produce hypotension after rapid bolus IV administration due to its alpha-blocking effects on the adrenergic receptor, leading to a decrease in systemic vascular resistance. Chlorpromazine is also a mild respiratory depressant (Sasada 2003).

The main therapeutic effect in PICU is sedation with flattening of behavioural responses allowing tolerance of the PICU environment in the agitated child. This is particularly useful in children who have become tolerant of multiple sedative drugs. Chlorpromazine enhances the effects of analgesics and lowers the seizure threshold. Despite its multiple side effects (that include extrapyramidal movements and cholestatic jaundice), chlorpromazine is generally well tolerated and safe. Chlorpromazine is well absorbed via the oral route, but there is extensive first-pass metabolism in the liver and gut wall so the bioavailability is only 30 %. The drug is mainly protein bound with primarily liver metabolism. The elimination half-life is 30 h (Sasada 2003).

39.3.2.4.2 Alimemazine (Trimeprazine)

Alimemazine has pharmacological actions intermediate to promethazine and chlorpromazine with marked antihistamine effects as well as central nervous system actions similar to chlorpromazine. This drug can provide significant sedation by intravenous or oral routes. It can produce mild hypotension by bolus IV administration and can lead to a prolonged QT interval. There is good oral bioavailability ranging from 70 to 100 % depending on the formulation. Oral dose of 2 mg/kg can be used for sedative purposes. It is 90 % protein bound in plasma and is extensively metabolised. The elimination half-life of alimemazine is 4–5 h (Sasada 2003).

39.3.2.4.3 Promethazine Hydrochloride

Promethazine is used in allergic conditions as well as for sedative and hypnotic purposes. It can be given intravenously as a bolus or infusion or

via the oral route. Oral availability is only 25 % due to a high first-pass metabolism in the liver with <1 % being renally cleared. It has a large volume of distribution (Taylor et al. 1983; Campbell et al. 1998).

Promethazine's antisialagogue effect can be useful if also using ketamine, which can increase oral secretions. Promethazine is a potent antiemetic that can also play a useful role if experiencing nausea as with high-dose opiates (Bui et al. 2002).

39.3.2.5 Butyrophenones

39.3.2.5.1 Haloperidol

Haloperidol's primary use is for schizophrenia and related psychoses. There is evidence for its use in patients in intensive care, particularly where agitation is a primary problem with a similar action to the phenothiazines. Some studies have reported its use as an infusion as well as bolus doses. The drug acts via the central dopaminergic blockade as well as postsynaptic GABA antagonism (Sasada 2003). It can be given intravenously, orally or intramuscularly. Oral bioavailability is 50–88 % with 92 % of the drug being protein bound. Metabolism is primarily by the liver with some of the metabolites being active (Sasada 2003). Haloperidol has minimal cardiovascular effects but can lead to hypotension in the presence of hypovolaemia. As with the phenothiazines, haloperidol is also an antiemetic.

Haloperidol induces a state where the patient has diminished motor activity, anxiolysis and indifference to the external environment. The advantage of this is that the patient will still be conscious and breathing – enabling weaning of ventilation, but the patient will remain calm (Riker et al. 1994). The other advantage of getting control of a patient who is severely agitated is that they then require fewer bolus doses of sedation, which put them at higher risk of accumulation before control is achieved and possible worsening withdrawal when they are finally extubated. There is minimal experience of the use of haloperidol in children.

One paediatric study of 40 patients looked at the concept of delirium in paediatric intensive

care. Neither haloperidol nor risperidone is registered for use in childhood delirium despite the fact that both drugs are frequently used for this reason in the adult population. Given the relatively high incidence of extrapyramidal symptoms with haloperidol, particular caution needs to be taken with specific consent prior to using this medication in PICU (Schieveld et al. 2007). Of the 40 children in the study with delirium, 27 were given haloperidol and 2 had an adverse reaction to it. All made a complete recovery from their delirium (Schieveld et al. 2007).

39.3.2.6 Clonidine

It is commonly given in PICU for its anxiolytic, analgesic and sedative properties as discussed in the analgesia section of this chapter. Clonidine can be given orally as well as intravenously with a bioavailability of 100 % via the oral route. Clonidine is 65 % renally excreted unchanged in the urine, 20 % excreted in faeces. The elimination half-life is 6–23 h. Renal impairment will markedly increase the time taken to clear the drug.

Clonidine is generally used as an opiate-sparing drug or for the treatment of opiate withdrawal on PICU. In addition to these uses, it can play a valuable role as an adjunct to aid sedation for those patients who are proving difficult to manage. In this context it can avoid the need to escalate the existing sedation a patient is on. A combination of opiate and clonidine – via the oral or rectal route – can be an effective combination in the paediatric setting.

39.3.2.7 Volatile Agents

39.3.2.7.1 Isoflurane, Sevoflurane, Halothane and Desflurane

The concept of using the volatile agents for longer-term sedation on ICUs is not a new one. Barriers in the past have been ways to safely deliver the drug (vapourisers) as well as protecting the staff and environment (scavenging systems). A few ICU ventilators in the past such as the servo 900c were able to provide a plug on vapouriser to deliver isoflurane to the critically ill patient, but these are now generally obsolete and have not been replaced.

Adult data has shown that isoflurane can be an effective and practical sedative drug in the intensive care unit when combined with opioids with few side effects (Spencer and Willatts 1992; Millane et al. 1992). More recently, Meiser and others have shown the rapidly eliminated inhalational agent desflurane to have characteristics that make it superior to other more conventional agents (Meiser et al. 2003). The data in PICU is very limited. The early ten patient study by Arnold et al. (1993) used relatively high doses of isoflurane as a single agent in patients who had already become tolerant to opioids. Their results showed that while the drug was effective, there was a high incidence (50 %) of tolerance agitation and dystonia on withdrawal of the drug. More recent reports, particularly for the treatment of status asthmaticus as part of a more balanced sedative regimen, have been more encouraging (Wheeler et al. 2000; Shankar et al. 2006). However, there is a major lack of good prospective data to evaluate the potential of these drugs in PICU.

In current practice paediatric inhalational agents need to be delivered via a standard anaesthetic machine with a ventilator or from an older Servo ventilator with vapouriser and while familiar to those with an anaesthetic background can be somewhat alien to paediatricians engaged in PICU. Another barrier to delivering inhalational sedation has been cost, but can be overcome by the use of closed loop circle systems. Newer techniques with purpose-built disposable inline vapourisers have shown promise (Berton et al. 2007). The *anaesthetic conserving device* (“AnaConDa”) has a charcoal absorber that confines most of the volatile agent within the patient circuit while also acting as a heat and moisture exchanger; this device is currently confined to adult practice.

Volatile agents can suppress EEG activity and act as potent bronchodilators, and in PICU these agents continue to be used selectively in some centres for treatment of status epilepticus and severe life-threatening asthma (Tobias 2008; Soukup et al. 2009). Given the major problems with intravenous sedation, the question is being asked as to whether volatile agents should be

reconsidered in PICU (Tobias 2000, 2008; Rohm et al. 2009) in a more widespread capacity. Advocates of inhalational sedation feel that because of its rapid elimination by the lung and the minimal metabolism within the body, it can confer more precision than the currently used drugs, allowing planned extubation and recovery and reduced PICU stay. In addition the drug can be used or modulated to incorporate painful procedures with rapid return to baseline sedation.

39.3.2.7.2 Xenon

The renewed recent interest in gaseous sedative agents is likely to continue with the developments of new delivery systems within ICU. Early studies with xenon show great potential in the clinical areas of the developing neonate and neurological injury (Sanders et al. 2004; Bedi et al. 2003). Unlike many PICU sedative agents including midazolam, ketamine and other volatile anaesthetic agents, xenon has been shown to provide anaesthesia and sedation in animal models without producing apoptosis (Ma et al. 2007). Further studies by the same group have also found that xenon can offer protection from hypoxic injury: they demonstrated that rat pups exposed to a hypoxic injury had a significantly better outcome with the combination of cooling to 32 °C in combination with xenon. The functional improvement with this regimen was almost complete, sustained long term, and accompanied by greatly improved histopathology (Hobbs et al. 2008). Issues still remain if this drug is to become viable in PICU. It is rare and expensive and requires a closed system of delivery, which necessitates new ventilatory systems to be developed.

39.3.3 Non-pharmacological Measures

39.3.3.1 Developmental Care

Other strategies have been employed in PICU to reduce susceptibility to pain and stress. The work in this area started in neonatal intensive care units before being implemented in PICUs. Developmental care concentrates on the child's

environment with concepts including reducing ambient noise and light, establishing day and night cycles and decreased handling (Franck and Lawhon 1998). Painful procedures are clustered together with adequate sedation. This is thought to lead to improved neuro-behavioural organisation, lower morbidity and earlier discharge from ICU (Als et al. 1986, 1994).

39.3.3.2 Sugar

In addition to the behavioural strategies mentioned above, there are other approaches that can be employed to reduce pain scores during painful procedures for infants in addition to visual and tactile senses. Taste can also be used to manipulate pain thresholds. Oral sucrose and sweet compounds are safe and effective at reducing pain scores. There is a dose-dependant effect from 5 to 50 %, but the optimal dose is not known (Stevens and Ohlsson 2000). Combining oral 10 % glucose with non-nutritive sucking and multi-sensorial stimulation (sensorial saturation) appears to have a greater effect at reducing the behavioural responses to pain sensations than any individual technique in isolation (Bellieni et al. 2001).

39.3.3.3 Nesting

Proprioceptive, vestibular and thermal stimulation occurs through swaddling, rocking and maintaining a flexed position (facilitated tucking) (Franck and Lawhon 1998).

39.3.3.4 Melatonin

Melatonin remains in the research domain. It is thought to help regulate the circadian rhythm, helping maintain a normal day-night routine (Seron-Ferre et al. 2001).

39.3.4 Assessing Adequacy of Analgosedation

39.3.4.1 Observational Measures

In order to assess pain and discomfort in PICU, physiological variables can be used. Heart rate, heart rate variability and blood pressure have

been used as a measure of sedation and analgesia with limited success (Owens 1984; Porter et al. 1988; Harpin and Rutter 1982). In addition patients with insufficient sedation can be found to have dilated pupils, and in the teenage population, they may sweat. Obviously a patient seen to grimace or fight against their endotracheal tube does not have sufficient sedation or analgesia.

In recent years there has been a move to find validated tools that allow a more formal way of assessing the adequacy of a patient's analgo-sedation.

Despite the current measures available, scores and the level of sedation remain non-linear in their relationship. Children receiving a sedative infusion may appear completely still and potentially oversedated until a threshold is reached. Once this "arousal threshold" has been exceeded, the child will rapidly become undersedated, requiring large additional doses to return to their pre-arousal state. This non-linear effect with sedative drugs and conscious level has been described in the adult population and prevents the use of sedation scores as predictive scores (Prys-Roberts 1987). Sedation scores are time consuming to perform and cannot be performed in the paralysed patient.

39.3.4.1.1 COMFORT Score

There are a variety of observational tools that can be used to objectively assess the level of sedation on PICU patients (Ambuel et al. 1992; Hannallah et al. 1987). The COMFORT score was specifically designed for use in ventilated paediatric patients with a scale of 0–40 and has been validated for use for all age groups including neonates (Ambuel et al. 1992; van Dijk et al. 2000). The COMFORT score looks at a variety of physiological and observed variables including agitation, movement and facial tension in addition to heart rate, blood pressure and respiratory response. Each dimension is rated from one to five with a target score of 17–26 for optimal sedation (Marx et al. 1994). The aim of the COMFORT score is to measure sedation levels and analgesia as a combination for paediatric patients and not just to a point pain as measured in many scoring systems.

39.3.4.2 Objective Measures

39.3.4.2.1 Electrophysiological Measures

39.3.4.2.1.1 Bispectral Index (BIS)/Auditory

Evoked Potentials (AEPs)/

Somatosensory Potentials (SSEPS)

Neurophysiological signals using cortical signals are potentially more specific ways of monitoring sedation than the physiological variables mentioned above. The brain's electrical activity is related to cerebral blood flow, cerebral metabolism and cerebral function, making it a candidate for monitoring sedation (Kuramoto et al. 1979). Two forms of cortical measurements are available which can correlate with consciousness. These are spontaneous electrical activity from the cortex (the electroencephalogram – EEG) and electrical responses, which are elicited by stimuli (the evoked potentials).

Analyses can be used to represent the EEG as a single variable, which has the possibility of being correlated with sedation, anaesthesia and sedative blood concentrations, assuming that the EEG is dependant on conscious state.

More recently, a higher-order frequency domain method using phase coupling (bispectrum – BIS) has been introduced as a commercial monitor in adults (Vernon et al. 1995; Liu et al. 1996). Even in adults it may still not always be predicative of an awareness reaction (Schneider et al. 2002). There are limited data of this monitor in children (Berkenbosch et al. 2002; Denman et al. 2000; Tobias and Berkenbosch 2001), and it cannot be used as an infallible tool to ensure that a patient is unconscious (Watcha 2001; Kussman et al. 2001).

Evoked potentials are a more sophisticated technique that elicits cortical response from auditory stimulation or from electrical stimulation of peripheral nerves (Sneyd et al. 1992; White et al. 1999).

Measurement of the auditory evoked potentials (AEPs) is a possible measure of depth of sedation and anaesthesia in adults using propofol anaesthesia (Tooley et al. 1996). AEPs have also been used to direct dosage regimens with propofol using derived knowledge of its pharmacokinetics (pharmacokinetic – pharmacodynamic

modelling). Somatosensory potentials (SSEPS), which are a more invasive technique, have potential as a tool for measurement of sedation, but data remains limited (Coulthard and Rood 1993).

39.3.4.2.2 Skin Resistivity

The idea of measuring skin resistivity is as a measure of the sympathetic nervous system. The principle being that any factor, such as pain or distress through lack of analgesia and sedation, will be reflected in an increase in sympathetic activity. With an increase in sympathetic activity comes an increase in activity of the skin nerves. This in turn leads to a filling of the sweat glands with a resultant reduction in skin resistivity. This skin resistance can be measured and used to quantify the level of sedation. Studies in paediatric patients have found it correlates well with the COMFORT score (Gjerstad et al. 2008).

As the comfort in part relies on observational measurements that include facial expression and spontaneous movement, it cannot be applied to paralysed patients. The role of measures such as skin resistivity is to provide a way of assessing levels of sedation in this difficult group. This currently remains a largely experimental area in the paediatric population.

39.3.5 Drug Weaning

39.3.5.1 Drug Holidays and Other Strategies

In the adult ICU, daily sedation holidays or holds are performed. All sedation is stopped until the patient is awake and able to follow commands. This gives a chance to assess the adequacy of sedation as well as an opportunity to assess the neurological status of the patient where appropriate. In the adult setting, the sedation is then restarted at half the initial rate.

In practice the daily sedation hold is not carried out to the same degree on PICU as children do not tolerate being awake and intubated to the point of following commands in the same way as an adult does. This strategy is occasionally used in older children, particularly those where

assessing neurology is key such as following a head injury.

In order to reduce the time and doses of sedatives required, the adult practice is often to insert a percutaneous tracheostomy at an early stage. This allows the patient to be ventilated while awake if a clinical decision is made that they are likely to require this degree of support for more than a few days. This also has the added benefit of allowing the patient to cough and clear their own secretions more effectively, reducing the risks of nosocomial chest infections. They will also be able to regulate their own breathing and therefore strengthen their respiratory muscles, helping to wean ventilatory support.

In children, the insertion of a percutaneous tracheostomy is a less frequent procedure. Technically it is a more challenging procedure with a smaller airway, which usually needs to be performed in theatre by an ENT surgeon opposed to by the intensivist on the ICU. The advantage of allowing the patient to be awake does not always apply in PICU, as often they will still require some sedation to tolerate being there attached to a ventilator and monitoring. When considering a paediatric tracheostomy, the care needs to be individualised to the patient.

Drug cycling is a useful tool in the intensive care environment. If a patient is showing signs of being undersedated despite adequate doses of drugs, the most appropriate way of achieving an optimal level of sedation is to change the current medications. Commencing a new sedative and analgesic agent opposed to further increasing the current drugs has the advantage of helping to avoid tolerance and withdrawal as well as gaining good control of their comfort. An example of drug cycling is illustrated in Fig. 39.1.

As soon as possible, converting to oral agents is preferable. Clonidine and oramorph are very well tolerated by the oral route, well absorbed and easily weaned over a prolonged period to minimise the withdrawal phenomena. The additional benefits of the oral route are less dependence on intravenous access and the ease with which these drugs can be administered in the ward environment.

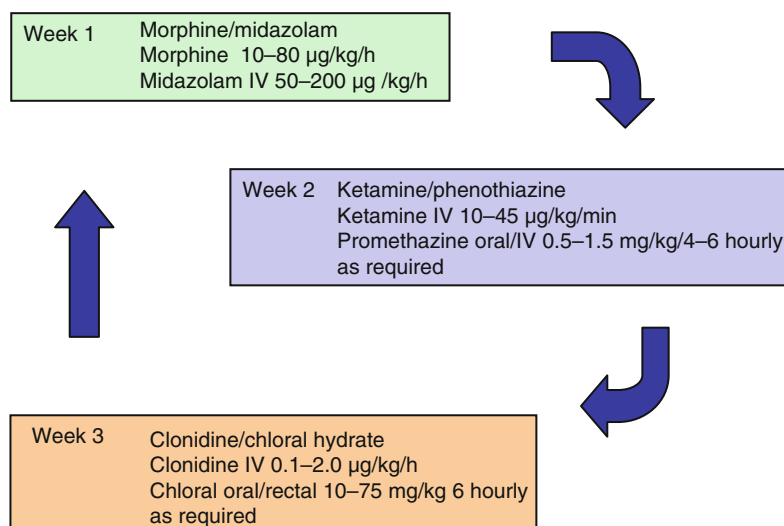


Fig. 39.1 An example of a sedation cycle. This scheme rotates the different classes of both analgesic and sedative drugs in order to try to minimise the onset and severity of drug tolerance. Immediately after surgery and throughout the first week, the first choice of drugs is an opioid with a benzodiazepine. If the patient remains intubated and ventilated at the end of the second week, the drugs are changed for an NMDA antagonist (ketamine) and an

antihistamine/phenothiazine (promethazine). If a third week is required, again a change is made to an alpha-2 agonist (clonidine) for analgesia and chloral hydrate as the hypnotic drug. Where possible oral medications are used in place of intravenous analgesic/sedative drugs. Dose adjustments need to be made for the bioavailability of the drugs and the effects of first-pass metabolism in the liver

39.3.6 Toxicity and Side Effects

The majority of the significant side effects are discussed with the individual drugs in the previous sections.

The most frequently occurring side effect from the sedatives is withdrawal from benzodiazepines. This can manifest as mild agitation to an unpleasant condition with some or all of the following: tachycardia, sweating, dilated pupils, “jitters” or possibly seizures, hallucinations and extreme agitation. Avoidance is the key with minimal doses while given as an infusion with cycling of drugs when necessary. The treatment is to keep the child in a quiet, dimly lit environment ideally with their parents. If environmental factors are not enough, then a weaning dose of oral lorazepam or clonidine can be very effective.

The NSAIDs carry the risk of inducing wheeze in asthmatic patients although not all children with this underlying pathology will be affected so it is worth asking the parents if they have had

these agents in the past. The more concerning side effect of the NSAIDs is renal dysfunction. In extreme cases renal failure can result. As patients in PICU are often fluid restricted with a degree of prerenal failure, caution is needed when prescribing these agents. Renal function and urine output must be closely watched after prescribing the drug, and if written for regular use, it must be reviewed on a daily basis.

39.4 Neuromuscular Blockade

39.4.1 Indications

In 1981, 91 % of British PICUs were using neuromuscular blocking agents frequently (Merriman 1981). Currently the use of these agents is higher than in adult ICUs, but as a specialty, we are now using blockade less frequently than we were. More recent reports estimate that long-term neuromuscular blockade is used in 14–16 % of

ventilated days in PICU. These children have a mortality rate of 18 % (Martin et al. 2001). The most commonly used agent is vecuronium, with atracurium and pancuronium being the next most frequent on UK PICUs (Playfor et al. 2007).

Neuromuscular blockade has multiple uses in the PICU. It is obviously used for patients that need to remain immobile for any reason, such as following tracheal reconstruction surgery. Other advantages to neuromuscular blockade include reducing the basal metabolic rate of the patient, for example, in those with severe cardiomyopathy. Neuromuscular blockade can be useful in patients that are difficult to ventilate, such as for inverse ventilatory ratios, for high-frequency oscillation or to deliberately hyper- or hypoventilate them depending on their underlying pathology (Playfor et al. 2007).

Certain procedures benefit from the patient being immobile: for example transporting children either between hospitals or investigations such as MRI. Occasionally uncooperative patients will be muscle relaxed to prevent loss of vital monitoring or invasive lines. In this group it is essential to aim for optimising their sedation and using neuromuscular blockade to achieve balanced anaesthesia.

Adequate analgesia and sedation should be obtained before commencing neuromuscular blocking agents. It is important to review the need for muscle relaxants regularly and discontinue infusions at least once every 24 h if clinically possible (Playfor et al. 2007).

39.4.2 Choice of Drug

39.4.2.1 Vecuronium

Vecuronium is a monotertiary, monoquaternary derivative of pancuronium that is the more potent agent of the two. Vecuronium has a slow onset of action, but in its favour, it has a relative lack of unwanted side effects regardless of dose. It is eliminated by the hepatobiliary route; some of the metabolites have neuromuscular blocking activity. These active metabolites are in part renally excreted which explains the accumulation seen in patients with renal dysfunction. Vecuronium has

a longer duration of action in children compared to adults as a result in differences in the drug's volume of distribution (Playfor et al. 2007).

39.4.2.2 Pancuronium

Pancuronium is a non-depolarising neuromuscular blocking agent with a long duration of action. It works by competitive antagonism of acetylcholine at postsynaptic nicotinic receptors at the neuromuscular junction. Up to 45 % of the drug is metabolised in the liver, with 50 % of the dose being excreted in the urine (80 % of this fraction as unchanged drug). It has sympathomimetic effects resulting in tachycardia and hypertension, which can be used as an advantage in maintaining the cardiac output of cardiovascularly compromised patients (Playfor et al. 2007).

39.4.2.3 Atracurium

Atracurium is a bisquaternary tetrahydropapaverum derivative from the benzylquinolinium family. Bolus doses of atracurium provide conditions suitable for intubation within 90 s of injection. The drug is broken down by two chemical mechanisms, Hofmann degradation and a non-specific ester hydrolysis that means there is no accumulation in patients with hepatic or renal failure. Clearance of the drug is temperature dependant with prolonged blockade in hypothermic patients, and conversely, it may be necessary to increase the dose if a patient becomes pyrexial. Clearance is faster in children than adults. It has no vagolytic or sympatholytic properties (Playfor et al. 2007). Atracurium, and to a lesser extent cisatracurium, results in significant histamine release. Due to the differing potency between the two agents, the risks of anaphylaxis with atracurium are higher. The level of histamine release with atracurium is often sufficient to cause hypotension, tachycardia or bradycardia (Playfor et al. 2007).

39.4.2.4 Cisatracurium

Cisatracurium was first used in clinical practice in 1996. It has a similar profile to atracurium in terms of cardiovascular stability. Cisatracurium has a slower onset of action but three to four times the potency of atracurium. As a result of

this, it is less likely to stimulate histamine release (Playfor et al. 2007). As with atracurium, cisatracurium is eliminated mainly by Hofmann degradation. On stopping an infusion of cisatracurium, it has been shown to allow the patient to recover neuromuscular function significantly quicker than with vecuronium (Burmester and Mok 2005). One group looked at children receiving an infusion of cisatracurium for longer than 24 h. They found that 29 % of the children required significantly increased doses, suggesting tachyphylaxis (Burmester and Mok 2005). The incidence of anaphylaxis is estimated at 1:10,000 for cisatracurium.

39.4.2.5 Rocuronium

Rocuronium has a rapid duration of action, approximately half the time of vecuronium. No rocuronium metabolites have been detected in the urine or plasma. As with vecuronium its excretion is primarily via the hepatobiliary route. Unlike vecuronium there is minimal alteration of the pharmacokinetics in the presence of renal failure. It can cause vagolysis in very high doses, but generally it has minimal cardiovascular effects. It is a non-depolarising blocker that, although has a quick onset, is still significantly slower than suxamethonium at laryngeal adductor paralysis. Rapid intubatable conditions can be achieved with a dose of 1 mg/kg (Playfor et al. 2007). Rocuronium is coming into favour for use in emergency situations due to its safety profile and the increasing availability of sugammadex that allows full drug reversal should it be necessary.

39.4.2.6 Suxamethonium

Suxamethonium is a neuromuscular relaxant with not only a rapid onset but also a rapid recovery (Rawicz et al. 2009). Although multiple side effects exist, they tend to occur in a relatively predictable manner. Bradycardia occurs rarely with a first dose of suxamethonium, but a second dose is associated with significant bradycardia so should be avoided if at all possible. Suxamethonium has been associated with hyperkalaemia-induced arrhythmia, and deaths have been linked to this side effect. This can be prevented with an injection of mivacurium (0.03 mg/kg) 2 min

prior to the administration of suxamethonium. Magnesium sulphate prior to administration can also help prevent hyperkalaemia without significant side effects (Rawicz et al. 2009).

Other recognised potential side effects of suxamethonium are malignant hyperthermia, masseter rigidity, fasciculation and muscle pain (rare in children). Additional side effects include increased cerebral blood flow that can in turn result in a rise in intracerebral pressure if the underlying pathology of the patient presents this as a risk. An increase in oxygen consumption and carbon dioxide production will also occur with suxamethonium (Rawicz et al. 2009).

The major lesson when considering the use of suxamethonium is to consider the patients underlying pathology and the skill of the intubator. Patients with advanced renal failure, late onset burns, some muscle wasting conditions or any other condition where hyperkalaemia is a risk are a contraindication to the use of suxamethonium. If possible it would be useful to have a family history to ensure malignant hyperpyrexia or prolonged blockade is not a risk, although history alone cannot exclude these possibilities. If you have a skilled intubator, the risks of a prolonged blockade are less, so alternative drug choices with a longer duration of action may be considered.

In less-skilled hands or where a difficult intubation is anticipated, the advantages of suxamethonium begin to outweigh risks as the short duration of action can be life-saving in a patient who you are unable to intubate or ventilate following blockade. With pharmacological advancement there are now alternatives to suxamethonium even in this group. As mentioned above rocuronium in large dose (1 mg/kg) has the ability to give intubating conditions as quickly as suxamethonium, allowing its use for rapid sequence induction. With the increasing availability of sugammadex, the ability to reverse the drug for patients that are found to be unintubatable now makes this drug a much safer alternative with far fewer side effects. Sugammadex also has the ability to reverse vecuronium, which although not suitable for a rapid sequence induction is a commonly used agent in paediatric intensive care.

Among the most important considerations when choosing a drug for intubation is a familiarity with whatever drug you use to ensure safe dosing and an awareness of the side effects. Being fully prepared for the intubation with adequate pre-oxygenation and airway adjuncts should you encounter difficulty is key. In situations where the intubation is not time critical and a difficult airway is anticipated, asking for expert help to allow, for example, the use of fibre-optic intubation can be very helpful.

39.4.3 Assessing Adequacy

There is no ideal way to monitor the adequacy of neuromuscular blockade in the paediatric ICU. Obviously any movements, eye opening or coughing can be observed from the bedside. A more subtle way of assessing paralysis is spontaneous respirations that will be recorded by the ventilator.

39.4.3.1 Train-of-Four (TOF) Monitoring

A more objective measure is with the train of four (TOF), a transcutaneous electrical stimulation, usually attached to stimulate the ulnar nerve. This is a measure frequently used in adults with an optimum trigger of one to two twitches being an acceptable level of blockade. In adult patients TOF has been used to reduce the total dose requirements for neuromuscular blocking agents allowing a faster recovery on cessation of medication. This permits patients to wake and extubate quicker with an earlier discharge from ICU, saving costs and potentially reducing morbidity with a shorter length of stay (Playfor et al. 2007).

This measure is difficult to do in infants as the forearm is small and direct stimulation of muscle groups can occur opposed to the desired nerve stimulation. Burmester et al. found that TOF stimulation allowed titration of neuromuscular blocking agents in the paediatric setting but that it was unreliable below 18 months of age (Burmester and Mok 2005). There can also

be effects to the readings from the TOF with tissue oedema, haemodynamic status, acid–base status and electrolyte disturbances (Playfor et al. 2007).

39.4.4 Drug Weaning

Muscle relaxants do not need to be weaned in the same way as sedation or analgesia. As a rule the patient is either required to be paralysed or not. It is important in PICU not to paralyse patients unnecessarily due to the side effects of the medications as well as paralysis itself. Units manage muscle relaxants in differing ways. Some units opt to run these agents as infusions and occasionally stop them, as a rule on a daily basis, to ensure adequate drug clearance and avoid accumulation of the agents.

Other units prefer to use bolus doses of muscle relaxants, this way enabling them to ensure accumulation cannot occur and forcing the team to reassess the need to continue paralysis with further doses. The risk of this strategy is destabilisation of the patient when the paralysis wears off, perhaps at an inopportune moment opposed to the greater level of control provided by an infusion. The risk with an infusion in an unstable patient is that if it is not stopped for several days, when finally stopped, it can take, in extreme cases, several days for the paralysis to fully wear off, overall slowing recovery.

The consensus standards from the Paediatric Intensive Care Society (PICS UK) suggest the use of vecuronium or atracurium by continuous infusion as the recommended agent for the majority of critically ill children requiring neuromuscular blockade on PICU. Intermittent dose of pancuronium may be considered (Playfor et al. 2007).

It is important to monitor sedation closely in the paralysed patient to ensure they are not awake or in pain while unable to communicate “aware”. A further advantage to breaks in paralysis allows not only clearance of the muscle relaxant but a chance to formally assess analgesia and sedation.

39.4.5 Toxicity and Side Effects

The risks of continuous paralysis in a PICU patient include that of unexpected extubation. This can occur in any PICU patient, for example, when they are turned or suctioned. In the case of a paralysed patient, the risks are highest as they will not be able to contribute any spontaneous breaths. If they are difficult to reintubate they are therefore at even greater risk, as the agent they are receiving may not be easily or rapidly reversed.

One major disadvantage of longer-term paralysis on PICU includes the chances of developing a critical illness myopathy as a result. Patients who make no spontaneous movements for days or weeks will get progressively weaker due to a lack of muscle activity and resultant myopathy. This can lead to a significant delay in discharge from PICU, not just as a result of poorer mobilisation but the deterioration in lung mechanics that evolves. Weakened respiratory muscles affect the ability to support respiration and tolerate extubation (Schindler et al. 1996).

Other than the weakening of respiratory muscles, the paralysed patient cannot cough. They are therefore unable to clear respiratory secretions and rely on suctioning down their endotracheal tube, which is not as effective as coughing. Failure to clear respiratory secretions puts the patient at risk of developing a ventilator-associated pneumonia, further increasing their morbidity and length of stay (Adnet et al. 2001).

The myopathy secondary to prolonged neuromuscular blockade also brings with it a risk of patients developing contractures. Pressure sores are also a danger for the immobile patient, hence the need for regular turning. A final hazard of prolonged paralysis is corneal drying that can result in permanent corneal damage if precautions are not taken (Playfor et al. 2007).

The neuromuscular blocking agents, as with other medications, have their side effects, which are discussed with the specific drugs in Sect. 39.4.2. For all these reasons, it is clear that paralysis should be stopped as soon as possible in PICU patients, relying on analgesia and sedation for control of interventions as far as possible.

39.5 Important Unknowns

39.5.1 The Current Dilemmas in Paediatric Practice

39.5.1.1 Immune Response to Anaesthetic Agents

Surgical stress leads to profound endocrine and metabolic changes that can influence the host defence response. The activation of the peripheral and central nervous system crucially initiates hormonal and metabolic responses to surgery. The afferent neural block with local anaesthetics is capable of reducing the stress response and associated immune changes. Anaesthetics directly cause immune suppression by influencing the functions of immunocompetent cells and inflammatory mediator gene expression and secretion (Kelbel and Weiss 2001).

Observations have shown impairment of the immune response by both anaesthesia and surgery with a high rate of infection and bone marrow depression after prolonged operations. This is seen as a decreased cell-mediated immunity from an impaired natural killer cell response and T helper 1 lymphocyte development. This T helper 1 reduction leads to preferential T helper 2 development (Helmy et al. 1999; Inada et al. 2004). Cell-mediated immunity is found to be depressed for 3–10 days postoperatively following major surgery. The same group also found that major surgery resulted in pro-inflammatory and anti-inflammatory components being stimulated. For patients who are already immunocompromised or septic, the implications of having major surgery are therefore even more significant than first thought.

The optimal prevention, and cure, of illness requires a balance between pro- and anti-inflammatory reactions. The immunomodulatory effects of some anaesthetics present a difficult balance, as modulation of immune function may be both beneficial and harmful. Relative immunosuppression may help reduce the inflammatory response that leads to SIRS after prolonged surgery. Conversely if the drugs impair the immune system too effectively, the patient is at increased

risk of developing nosocomial infections in the recovery phase, prolonging their intensive care stay (Kelbel and Weiss 2001).

39.5.1.2 Apoptosis and Neurotoxicity

Bosch et al. published the first evidence that anaesthetic agents could be toxic to the developing brain in *Science* in 1999. Following that original work and multiple animal models published since, the concept of neurotoxicity from anaesthetic and sedative agents has been established. The majority of work has been published in rats and illustrates that there is a window in neurodevelopment during which the brain appears to be particularly vulnerable to external factors. This early neuronal pathway development appears to be governed by a combination of NMDA receptor and GABA receptor interactions. The fact that the majority of drugs in question act at these receptors explains why such a broad selection of drugs can give such a reproducible pattern of neural upset in the animal models. More recent work building on the original rat models highlights that specific combinations of drugs can have a worse effect and, in certain instances, lead to longer-term neuronal changes affecting development and behaviour in later life (Loepke and Soriano 2008; Loepke 2010).

The major difficulty is proving if this work is representative of human neonates and infants. The comparable time course when the most damaging effects would occur in humans is estimated to be from the third trimester to anywhere from 1–3 years of age. It is clear to see that this covers a large proportion of the children on paediatric intensive care units (Loepke and Soriano 2008; Loepke 2010).

Animal studies have told us that exposure to sedatives and anaesthetics can increase apoptotic cell death up to 68-fold (Loepke 2010). What we cannot know is could this reflect a speeding up of cells that were destined to be destroyed anyway – premature physiological apoptosis – or is it death of cells that would have survived without the external influence of pharmacology, pathological apoptosis (Loepke and Soriano 2008; Loepke 2010; Creeley and Olney 2010; Istaphanous and Loepke 2009)? The bigger question being what effect does this have on

the developing brain and will that child go on to reach their full potential or will they suffer an impairment in function – however subtle. There are so many confounding variables to these questions that the small numbers of studies on human subjects have been unable to definitively answer.

The mechanism behind this accelerated apoptosis is thought to relate to anaesthesia-induced GABA receptor activation and NMDA receptor blockade. Combinations of drugs acting at both receptors are felt to be even more damaging with higher levels of apoptosis than with single agents (Loepke and Soriano 2008; Istaphanous and Loepke 2009). This theory has been proved correct in animal models. The combination of GABA-mimetic drugs such as volatile agents or propofol with NMDA antagonists such as nitrous oxide or ketamine renders the developing brain even more susceptible to apoptotic neurodegeneration (Loepke and Soriano 2008).

The only human studies are a collection of case series looking at the link between anaesthesia and sedation with behavioural and developmental changes later in life. A retrospective review of the New York State medical database using a cohort of 229,000 children suggested that those who had undergone a hernia repair before the age of 3 years were nearly twice as likely to be diagnosed with developmental behavioural disorder than a comparative cohort of 5,000 individuals (Istaphanous and Loepke 2009).

A second American study looked at more than 5,000 children who were exposed to two or more anaesthetics before the age of 4 years. These children were more than twice as likely to be diagnosed with learning difficulties compared to controls (Loepke 2010; Istaphanous and Loepke 2009). Although these studies suggest a relationship between surgery and behaviour in later life, none of them can eradicate the confounding factors of surgery, postoperative pain or inflammation from the effects of anaesthesia on the developing brain (Istaphanous and Loepke 2009).

While it is clearly concerning that a large group of drugs that we use on a regular basis in PICUs are potentially neurotoxic, it is important to remember that there is also good evidence for

deleterious effects from painful stimuli and stress. These negative experiences can lead to increased stress hormone levels, altered pain thresholds, abnormal behaviour as well as neuronal cell death (Loepke and Soriano 2008). In one study ketamine anaesthesia during painful procedures was found to ameliorate the deleterious effects associated with the pain, without causing neurodegenerative effects (Loepke and Soriano 2008).

This growing body of evidence points to at least a temporary neurological dysfunction after early life exposure to anaesthetics. As the effects of pain and stress can also be damaging, there is no way to withhold these medications in our patient group, and therefore, we need to be meticulous with our dosing and use adjuncts such as regional anaesthesia where appropriate (Loepke and Soriano 2008). Combined administration of GABA agonists and NMDA antagonists should be avoided where possible in view of the current evidence. Care must of course be taken to optimise haemodynamic stability and avoid hypoxia, as these are the main ways to avoid neurological impairment (Loepke and Soriano 2008).

Essentials to Remember

- Drug selection and dosing needs to include thought on likely duration of administration and side effect profile in relation to the pathology and age of the child.
- No drug is free from complications – consider the risks and benefits and review regularly.
- A moving child does not necessarily indicate discomfort.
- Optimise drug delivery to avoid tolerance and withdrawal.
- Monitor the effectiveness of drugs, with a regular review of need and dose. If muscle relaxants are used, regular paralysis holidays are advisable.
- Drug cycling may maintain control and prevent accelerated tolerance.

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Part XIV

A Practical Approach to Noninvasive Mechanical Ventilation

Amir Kugelman

Educational Aims

- To know how to initiate NRS and to adjust the ventilator settings during NRS therapy
- To be familiar with the possible short- and long-term side effects of NRS
- Practical hints for neonatal NRS application
- To recognize failure criteria of NRS
- To understand the process of weaning from NRS

nasal intermittent mandatory ventilation (NIMV) is commonly used, with considerable variability in the techniques applied (Owen et al. 2008). The wide range of clinical approaches highlights the paucity of evidence available. More evidence is needed to establish the best practice (Owen et al. 2007, 2008). Data on term infants are lacking and we will focus on preterm infants. The following suggested practical approach is based on the current literature.

40.1 Nasal Respiratory Support: Introduction

Different approaches to noninvasive nasal respiratory support (NRS) are used today in different centers (Fig. 40.1). Owen et al. just recently concluded that in the practical approach in England,

40.1.1 Initiating Nasal Respiratory Support (NRS)

40.1.1.1 Nasal Continuous Positive Airway Pressure (NCPAP)

Nasal continuous positive airway pressure (NCPAP) goal in infants with respiratory distress syndrome (RDS) is to maintain lung recruitment or functional residual capacity (FRC). The level of pressure should achieve this goal without compromising circulatory or ventilatory function (Yu and Rolfe 1977). A pressure of 4–6 cm H₂O usually will be adequate (Kugelman et al. 2007; Barrington et al. 2001; Khalaf et al. 2001; Friedlich et al. 1999). Meta-analyses of CPAP studies suggest that a pressure of at least 5 cm H₂O is needed to provide benefit over ambient oxygen (Moretti et al. 1999). Higher pressures up to 8 cm H₂O were used by some investigators, but at least in one study, the rate of pneumothorax

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Fig. 40.1 Nasal respiratory support via nasal prongs



using such pressure was relatively high (Morley et al. 2008).

Practical comments regarding different NCPAP devices will be discussed in Sect. 40.1.5.

40.1.1.2 Nasal Intermittent Mandatory Ventilation (NIMV)

The ventilator settings used for NIMV or nasal synchronized intermittent mandatory ventilation (NSIMV) were not similar in all studies. The effects of different initial settings on the success of NIMV and of manipulating the settings on clinical status have not been investigated.

No study has investigated the optimal level of positive end-expiratory pressure (PEEP) during NIMV. It is probably adequate to adopt the recommendations for NCPAP, as CPAP to maintain FRC in treating RDS is the basis for NRS and the intermittent mandatory ventilations used in NIMV are just added on top of the CPAP.

No studies have investigated optimal peak inspiratory pressure (PIP) during NIMV. Some NIMV studies used a PIP similar to that used during ventilation (Friedlich et al. 1999; Moretti et al. 1999), whereas others used pressures 2–4 cm H₂O higher than pre-extubation PIP (Khalaf et al. 2001; Santin et al. 2004). One study used enough pressure “to see the chest rise” (Lin et al. 1998), and others chose specific target pressures (16–20 cm H₂O) (Barrington

et al. 2001; Ryan et al. 1989). Ryan et al. (1989) noted that despite a set pressure of 20 cm H₂O, the pressure generated at the proximal end of the nasal prongs was highly variable (range 8–21 cm H₂O; mean 10 cm H₂O).

The optimal rate of inflation during NIMV has not been investigated. A range of rates have been used, mainly 10–25/min. There were reports on the use of assist control mode, in which every infant-initiated breath is supported by a ventilator inflation (Ali et al. 2007). No studies have investigated the flow to use in the circuit during NIMV. The circuit flow, and the leak from the device, will influence the PIP achieved during each inflation.

We suggest choosing the initial ventilator settings according to the indication for NIMV. For the initial treatment of RDS (Kugelman et al. 2007), NIMV was set at a rate of 12–30 breaths per minute (according to PaCO₂), inspiratory time of 0.3 s, positive end-expiratory pressure of 6 cm H₂O, and PIP of 14–22 cm H₂O according to chest excursion and the infant’s weight. FiO₂ was set to keep adequate oxygen saturation by pulse oximetry. Ventilator settings after extubation were those used for endotracheal ventilation prior to extubation in some studies (Khalaf et al. 2001; Friedlich et al. 1999; Moretti et al. 1999) or only “sigh” ventilation in other studies (Barrington et al. 2001).

40.1.1.3 Nasal Flow

Nasal cannulae have been used to deliver oxygen at flow rates of 0.5 l/min to as high as 6 l/min, usually with no intention of delivering CPAP. However, a significant amount of CPAP is generated (“inadvertent CPAP”) and is not measured continuously at the bedside (Locke et al. 1993). One must exercise caution when delivering flow rates greater than 2 l/min via nasal cannula without knowing the amount of pressure delivered. This is also true for the warmed and humidified new delivery systems. Nasal cannula at flows of 1–2.5 l/min can deliver positive distending pressure in premature neonates (Sreenan et al. 2001).

Kubicka et al. (2008) concluded that HFNC therapy using cannulae of 0.2-cm outer diameter can generate some level of CPAP when the mouth is closed. The amount of pressure generated was related to the flow rate, the size of the leak around the nasal cannula, and the degree of mouth opening. They estimated the levels of CPAP created by HFNC by measuring oral cavity pressures. They also raised the important safety and monitoring issues for the use of these devices. They speculated that if the nasal leak is eliminated with the use of cannulae that obstruct the nares completely, then dangerously high distending pressures may be generated when the mouth is closed. Thus, they suggested that HFNC therapy should not be used as a routine replacement for CPAP therapy.

Standard or low-flow nasal cannula is limited by inadequate humidification and unheated air flow. Delivery of such a gas may lead to airway dysfunction and negative respiratory outcomes. Cooling and loss of water from the airways may impair mucociliary transport, increase fluid osmolality, promote bronchospasm, and increase the viscosity of airway secretions. Moreover, considerable energy is required to heat and to humidify gas delivered into the nose, potentially interfering with optimal nutrition and growth (Waugh and Granger 2004; Schulze 2002). On the basis of studies with very low birth weight (VLBW) infants undergoing ventilation, the delivery of nonhumidified gas may lead to increases in air leaks, more severe chronic lung disease, impaired surfactant activity, and changes in pulmonary mechanics (Tarnow-Mordi et al.

1989; Shelly et al. 1988). Delivery of cold, relatively dry gases, particularly at high flow rates, to the nose may also lead to nasal mucosal injury and bleeding, resulting in pain and creating a portal of entry for infectious agents. The warmed and humidified new delivery HFNC devices overcome the disadvantages of commonly used nasal cannula therapy, in which the delivered gas is well below body temperature and only partially humidified (Kubicka et al. 2008).

40.1.2 Ventilator Settings Adjustments During NRS Therapy

40.1.2.1 Nasal Continuous Positive Airway Pressure (NCPAP)

NCPAP pressure may be weaned in the recovery stages of RDS as lung compliance improves to avoid overdistension. Pressures may be increased for lung recruitment in severe RDS (usually up to ~8 cm H₂O) while monitoring the hemodynamic effects in the individual patient and chest radiograph to avoid hyperinflation. When treating the acute phase of RDS in the very premature infant, one should consider intubation and surfactant administration instead of increasing the CPAP level. We wean infants to spontaneous unsupported breathing from 4 to 6 cm H₂O. We usually do not use lower pressures.

40.1.2.2 Nasal Intermittent Mandatory Ventilation (NIMV)

The setting of NIMV during the time the infant requires NRS is adjusted to maintain the goals of adequate oxygenation and ventilation (permissive hypercapnia). Oxygenation is maintained by FiO₂ and mean airway pressure (inspiratory time [IT], peak inspiratory pressure [PIP], and CPAP level) and ventilation by the respiratory rate, expiratory time, PIP, and maintaining adequate CPAP, according to the rules of conventional endotracheal ventilation. Yet, this routine was not tested in controlled trials. For example, no study has shown that higher rates on the ventilator change the PaCO₂, while the baby is breathing spontaneously and complements the NRS. Yet, increasing the

rates may decrease the work of breathing. Meta-analysis of two trials comparing NIMV and NCPAP in infants with apnea demonstrated no difference with regard to carbon dioxide levels after 4–6 h of support (Lemyre et al. 2002). Nasal ventilation respiratory settings need to be further studied to allow evidence-based recommendation.

40.1.2.3 Nasal Flow

Oxygen should be monitored to keep the required oxygen saturation. An oxygen/room air mixer may be required to assure limitation on the higher level. The CPAP created at different flows of HFNC needs to be studied to guide a controlled use, if one's intention is to create CPAP with nasal flow. There are fluctuations that are not continuously measured, and this may create obstacles in using formulas created according to flow, gestational age, and weight (Kubicka et al. 2008). Certainly, a high flow limitation should be kept to avoid the complications of air leak.

40.1.3 NRS Failure Criteria

Criteria for failure of nasal support differ between studies (Kugelman et al. 2007; Barrington et al. 2001; Khalaf et al. 2001; Friedlich et al. 1999). The criteria used in the study of Kugelman et al. (2007) for the initial treatment of RDS were clinical deterioration [increased respiratory distress] accompanied by at least one of the following or worsening of the following: pH <7.20 and PCO₂ >60 mmHg, PaO₂ <50 mmHg or arterial oxygen saturation by pulse oximetry (SpO₂) <88 % on FiO₂ >50 %, and recurrent significant apnea requiring repeated stimulation or bag-and-mask ventilation despite the use of methylxanthines or adequate nasal support (proper ventilatory settings and no technical problems). It is possible to switch from NCPAP to NIMV in order to try to minimize endotracheal intubation.

40.1.4 NRS Side Effects

40.1.4.1 Short-Term Side Effects

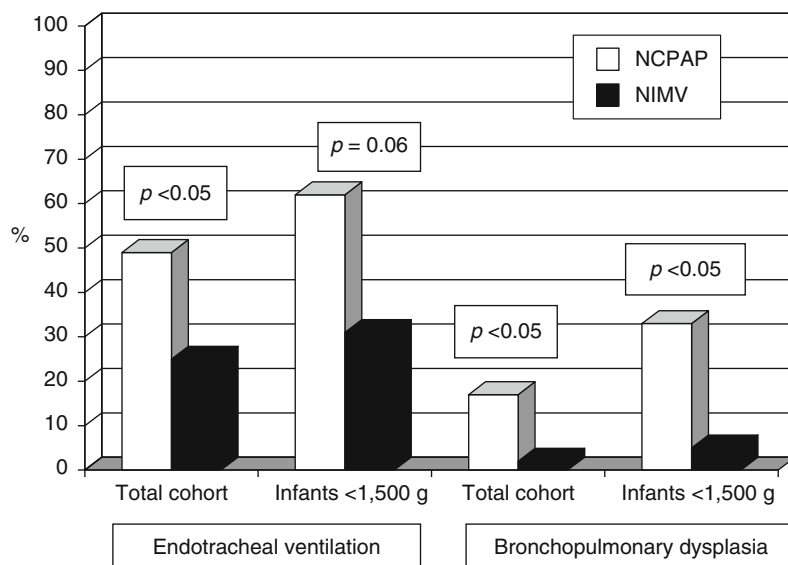
NRS seems to be safe. Of some concern is the study of Morley et al. (2008) that reported higher

incidence of pneumothorax (9 %) in the CPAP group (8 cm H₂O), as compared with 3 % in the intubation group ($p < 0.001$). However, other studies did not report such high rates of pneumothorax on NCPAP or on NIMV (Kugelman et al. 2007; Barrington et al. 2001; Khalaf et al. 2001; Friedlich et al. 1999; Moretti et al. 1999; Santin et al. 2004; SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al. 2010). There was a concern that NIMV might cause more gastrointestinal complications than NCPAP because of gastric distension leading to cessation of feeds or perforation (Sreenan et al. 2001; Garland et al. 1985). However, no gastrointestinal complications were reported in other studies, and time to full feeds was similar in the two methods (Kugelman et al. 2007; Barrington et al. 2001; Khalaf et al. 2001; De Paoli et al. 2003; Davis et al. 2001).

The discomfort related to NRS may be of importance and deserves our attention for two main reasons. First, our aim is to be gentle and to keep a policy of “minimal handling” in the care of premature infants. Second, an irritable infant who “fights” the NRS may be exposed to a higher risk of pneumothorax (Morley et al. 2008). Thus, we have to be aware of the immediate discomfort and possible short- and long-term effects, developmental or hearing problems arising from our treatment.

NRS may irritate the infants because the nasal flow causes high noise levels (Surentheran et al. 2003; Karam et al. 2008). Surentheran et al. reported mean noise intensity in the ear at 1 kHz of 55 dB, higher on NCPAP compared with spontaneous breathing or conventional ventilation, and up to 102 dB at some frequencies (Surentheran et al. 2003). In another study (Karam et al. 2008), mean noise level was 88.6 (SD 18.8) dB and was correlated with flow ($p < 0.01$) but not with pressure. A noise level above 90 dB was detected in 67 % of the measurements. NRS may cause pain and irritation in relation to nasal flow, high pressure in upper airways and local pressure, and trauma (Shanmugananda and Rawal 2007; Yong et al. 2005). Adequate techniques for fixation of the NRS devices that minimize the friction and direct pressure on the nose may decrease these undesired local effects. Devices that deliver

Fig. 40.2 Endotracheal mechanical ventilation and bronchopulmonary dysplasia (BPD) in infants treated with NIMV and NCPAP (Reproduced with permission from Kugelman et al. (2007))



humid and warm nasal flow were shown to reduce the rate of nasal mucosa injury as compared to standard HFNC (Woodhead et al. 2006).

NRS may affect physiological parameters during RDS and while the babies are stabilized, at the phase of recovering from RDS. Yu and Rolfe (1977) concluded that with correct use of NCPAP, an improvement in oxygenation generally occurs without obvious adverse cardiorespiratory effects. However, when appropriate pressures are exceeded, it is possible that both circulatory and ventilatory function might be severely compromised, possibly by overdistension and a decrease in the venous return. Kugelman et al. (2008) concluded that NRS in “stable” premature infants is associated with increased blood pressure and increased discomfort, despite a decreased respiratory rate. The clinical importance of these effects was modest. While these findings are reassuring when NRS is needed, they should be considered when the medical team balances its need and advantages with its adverse effects according to the clinical condition of the infant. To minimize the discomfort related to NRS, we should shorten its use when possible.

40.1.4.2 Long-Term Side Effects

The main goal of NRS is to administer gentle respiratory assistance to premature infants with RDS with avoidance of endotracheal ventilation.

NIMV as the initial mode of ventilation was shown to reduce the rate of BPD (Kugelman et al. 2007) (Fig. 40.2). This study was limited by the small sample size of infants <1,500 or <1,000 g. Thus, the results of the study regarding BPD in VLBW infants should be taken with caution. A plausible explanation for the decreased rate of BPD in the NIMV group in this study could result at least partially from the reduced rate of endotracheal ventilation in this group. Previous studies have shown that the lowest incidence of BPD occurred in NICUs practicing early NCPAP instead of initial mechanical ventilation (Avery et al. 1987; Van Marter et al. 2000). Morley et al. (2008) studied infants who were born at 25–28 weeks gestation. While at 28 days there was a lower risk of death or need for oxygen therapy in the CPAP group than in the intubation group, at 36 weeks gestational age, 33.9 % of the infants who were assigned to receive CPAP had died or had bronchopulmonary dysplasia as compared with 38.9 % of infants who were assigned to receive intubation ($p=0.19$). In the SUPPORT study (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al. 2010), 1,316 infants born between 24 0/7 weeks and 27 6/7 weeks of gestation were randomly assigned to intubation and surfactant treatment (within 1 h after birth) or to NCPAP treatment initiated in the delivery room, with

subsequent use of a protocol-driven limited ventilation strategy. They found that “Death or BPD” in the NCPAP vs. surfactant groups did not differ (47.8 % and 51.0 %, respectively). To note, in these studies infants were treated initially with NCPAP and not with NIMV. On the other hand, a trend towards lower rate of BPD in NIMV compared to NCPAP, not reaching statistical significance, was reported in studies comparing the two modes at the post-extubation period (Barrington et al. 2001; Khalaf et al. 2001; Davis et al. 2001). Another retrospective study showed that the number of infants with BPD was significantly less when they were extubated to NSIMV compared to NCPAP (73 % versus 40 %; $p < 0.01$) (Kulkarni et al. 2006).

Information regarding the neurodevelopmental long-term outcome of ELBW infants treated primarily with NRS is limited. Hansen et al. (2004) studied 269 surviving children with birth weight below 1,000 g or gestational age below 28 weeks born in Denmark between 1994 and 1995. They found that the intellectual development of children in this cohort treated with early nasal CPAP did not suggest a higher proportion of adverse effects on the brain compared to the published follow-up studies of preterm children treated with mechanical ventilation. However, in their population-based cohort, the survival rate for infants below 25 weeks of gestation was relatively low, and this may indicate a limit for the use of early nasal CPAP. Wintermark et al. (2007) studied infants weighing <1,500 g or <32 weeks of gestational age, at 6 and 18 months corrected age and at 4 years of age. They concluded that the developmental outcome did not show any harmful effect of early application of NCPAP to treat respiratory failure in VLBW infants. Bhandari et al. (2007) comparing ~20 infants on conventional ventilation to those extubated to NSIMV (birth weight: 600–1,250 g) found no differences in the mental or psychomotor developmental index scores on follow-up between the two groups. Yet the number of infants participating in the follow-up was small (~7 in each group). A retrospective study by Stack and Jalaludin (2007) found that a CPAP approach to the management of initial respiratory

disease in premature babies of less than 32 weeks gestation at birth is associated with no measurable developmental advantage or disadvantage at 2 years of age.

Thus, it seems that NRS may be beneficial in terms of preventing BPD and safe in terms of neurodevelopmental outcome. However, additional long-term follow-up of patients enrolled in randomized studies is needed to confirm this conclusion.

40.1.5 Practical Hints for Neonatal NRS Application

Different techniques of NRS are available. Short binasal prong devices are more effective than single prongs or nasopharyngeal prong (De Paoli et al. 2008). Infant flow driver uses a fluidic flip system that has been shown to assist spontaneous breathing and reduce work of breathing by reducing expiratory resistance and maintaining a stable airway pressure throughout the respiratory cycle. It was also shown to provide better lung recruitment compared to continuous flow NCPAP (Courtney et al. 2001; Pandit et al. 2001). However, the infant flow driver was found to be as effective as conventional CPAP in preventing extubation failure among ELBW infants (Stefanescu et al. 2003).

Bubble CPAP is accomplished by submerging the expiratory limb of respiratory circuit within a fluid column. The amount of pressure maintained within the system is determined by the depth of submersion and is generally independent of flow rate. Bubble CPAP may be more successful than the standard CPAP (Pillow et al. 2007; Koyamaibole et al. 2006; Narendran et al. 2003). Bubble CPAP may also provide an inexpensive form of CPAP with some characteristics of non-invasive high-frequency ventilation (Pillow et al. 2007; Lee et al. 1998). In a randomized crossover trial (Morley et al. 2005), 26 babies treated with nasal prong (CPAP) from a bubbling bottle received vigorous, high amplitude, or slow bubbling for 30 min. Pulse oximetry, transcutaneous carbon dioxide, and respiratory rate were recorded. The bubbling rates had no effect on

carbon dioxide, oxygenation, or respiratory rate. Finally, there are different methods that try to synchronize NIMV. However, while NSIMV may be preferred over NIMV, this was not demonstrated, and synchronization is probably not mandatory (Kugelman et al. 2007).

Good quality nursing during NRS care is of uttermost importance. The success of the treatment relies on optimal positioning of the baby, maintaining patency of the upper airways, and avoiding loss of the positive airway pressure. Key points for NRS nursing care according to Bohlin et al. (2008) and our own experience: keep an open nasal passages; find the optimal comfort body position for the infant and keep the head in mild extension to keep an open airway with a neck support; use preterm pacifier to minimize loss of pressure from open mouth or keep the mouth close with chin support to achieve adequate CPAP; try to avoid suctioning the nose and use saline drops instead and then suction the oropharynx; use adequate humidification and temperature of gases; avoid using excessive force when fixating the nasal prongs; do not pull tightly the nosepiece against the nose and keep it under the nose; protect the nose with manufactured or “homemade” materials; use the largest size prong that will sit without support in the nose; inspect the fixation when you see that the nosepiece is pressing too tightly against the nose or the NRS pressure is difficult to hold; and change to a larger prong as the baby grows. Some studies suggested using a gastric tube, open to air, to avoid gaseous distension of the stomach during NIPPV (Friedlich et al. 1999; Kiciman et al. 1998), although there is no evidence that this works. We remove the air from the stomach at least twice every 8 h to avoid overdistension.

40.2 Weaning from Noninvasive Respiratory Support in the Premature Infant

Length of NIMV depends on the indication (RDS or apnea), gestational age, weight, and possible side effects, and there are no clear guidelines as

to when to stop NRS. Infants with RDS were allowed to stop NRS (to only oxygen or low nasal cannula flow [<1 l/min]) when on $\text{FiO}_2 < 30\%$, with normal blood gases and with no respiratory distress or apnea as evaluated by the attending neonatologist (Kugelman et al. 2007).

Two approaches to weaning from NRS are possible. The first is to wean pressures and rate as performed while on conventional ventilation, weaning first those parameters that may cause lung damage. The second approach is to use cycles of NRS and spontaneous breathing and allow exercising the respiratory muscles. Weaning by slowly reducing CPAP pressures has been shown to be superior to weaning by time pauses, often referred to as “training” the infant off CPAP (Singh et al. 2006). Logically, pausing can result in alternating hyperinflation with collapse of alveoli (atelectato-trauma) known to be associated with development of BPD. No studies have compared strategies for weaning from NIMV. In the studies reviewed in this article, infants were weaned according to clinical and blood gas criteria, by reducing rate, pressure, and inspired oxygen.

The preferred method of weaning from NRS needs to be studied. The way to wean from NRS may be important, but it is possible that this issue has a neglected role in the final outcome.

Essentials to Remember

- Maintaining FRC is essential for the treatment of RDS in all modes of NRS.
- Data on ventilator settings on NRS needs to be further studied for effective and safe use.
- NRS is safe. However, possible side effects should be monitored and prevented.
- NRS is beneficial, but when the infant is “ready” to wean, try to take him off NRS.
- The comfort of the infant needs to be maintained while on NRS.

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Educational Aims

- Recognise continuous positive airway pressure (CPAP) support and noninvasive positive pressure ventilation (NPPV) as important modalities of respiratory support in children and infants with acute respiratory failure (ARF).
- Know the indications and technical issues to initiate and perform CPAP and NPPV.
- Understand the importance of a good knowledge of patient interfaces, ventilators as well as continuous medical and nursing education to ensure CPAP and NPPV success.

Noninvasive ventilation (NIV) refers to all respiratory supports that do not require endotracheal interface. Continuous positive airway pressure (CPAP) support and noninvasive positive pressure ventilation (NPPV) are the most frequent techniques encountered. During the last decade, NIV has been increasingly used in paediatric patients. However, little has been written in the paediatric setting. Most of the reported experience originates from adults.

41.1 Continuous Positive Airway Pressure

Sandrine Essouri

Continuous positive airway pressure experience is mostly derived from retrospective or small clinical studies. Reported results either include a few patients or focus on a single disease. As a result, evidences are lacking in order to define indications, techniques and complications of CPAP in children. Indeed, physiological response of infants and children to acute respiratory failure (ARF) cannot be extrapolated from adults, as shown later on.

41.1.1 Indications

The first published experience, in the early 1970s by Gregory et al., of CPAP in the management of respiratory distress of the newborn launches a new era of ventilatory support in the youngest

Table 41.1 Clinical studies published on continuous positive airway pressure (CPAP)

	Main primary diagnosis	Age (months)	Weight (kg)	CPAP level (cm H ₂ O)	CPAP duration (days)	CPAP failure (n)
Larrar et al. (2006) (n=53)	Bronchiolitis	1.4	3.7	5 à 8	2.7	13
Campion et al. (2006) (n=69)	Bronchiolitis	1.6	3.9	4 à 8	2	12
Codazzi et al. (2006) (n=15)	Post-extubation	24		5–10 (helmet)		2
Thia et al. (2008) (n=31)	Bronchiolitis			5 à 6		
Cambonie et al. (2008) (n=12)	Bronchiolitis	1.4	3.6	6		0
Martinon-Torres et al. (2008) (n=12)	Bronchiolitis	4.7		7.2±1.2		0
Javouhey et al. (2008) (n=27)	Bronchiolitis	1.3		5 à 10	2.2	
Mayordomo-Colunga et al. (2009) (n=78)	Bronchiolitis, asthma	8	8	6.7±1.2		6

Characteristics of patients and CPAP support

patients (Gregory et al. 1971). Ventilatory support used by paediatric intensive care units during the last decades reveals that CPAP was rarely used outside the neonatal period and the chronic condition. Specific technical concerns, such as the lack of interface, have hindered for a long time CPAP application in the population of the 3–10 kg of body weight. Moreover, the need to maintain a constant pressure during the entire cycle and uncontrolled air leaks has limited the potential benefit of CPAP technique (Gherini et al. 1979). The recent development of devices able to convert the kinetic energy of a jet of gas into a stable airway pressure has allowed the use of CPAP in the youngest (Moa et al. 1988; Klausner et al. 1996). The main aetiology of acute respiratory distress failure in patient of less than 1 year old is lower respiratory tract infections, mainly due to acute viral bronchiolitis. Beasley et al. described for the first time the use of CPAP in the management of 24 patients with severe bronchiolitis with a significant improvement in respiratory rate and gas exchange (Beasley and Jones 1981). During the 1990s, similar benefits were demonstrated by Soong et al. in further ten infants with severe bronchiolitis treated by nasal CPAP (nCPAP) (Soong et al. 1993). Using the Benveniste device (either mononasally or binasally) as a first inten-

tion ventilatory support, Kristensen et al. showed that in severely ill infants with viral bronchiolitis a reduced requirement of mechanical ventilation (1.3 %) when compared to previous studies from North America using invasive ventilation as a first support (Kristensen et al. 1998).

In the early 2000s, new interfaces (nasal prongs), which could be used in children over 3 kg of body weight, became commercially available. The nasal prongs facilitated noninvasive pressure support implementation to infants with severe bronchiolitis.

The helmet NIV interface, first developed for the adults, was recently available for children, with the new “baby body” (CaStar; Starmed, Mirandola, Italy), and used for nCPAP implementation in various aetiology of acute respiratory failure (Piastra et al. 2004, 2009).

In the last 5 years, several clinical studies have reported their experience in management of bronchiolitis with nCPAP (Campion et al. 2006; Larrar et al. 2006; Martinon-Torres et al. 2006; Cambonie et al. 2008; Thia et al. 2008). These studies are resumed in the Table 41.1. All studies showed an improvement in breathing pattern, and gas exchange, as well as a low rate of intubation. In addition, nCPAP has been shown to decrease respiratory muscle load in children with upper

Table 41.2 Clinical studies on severe acute bronchiolitis with nasal CPAP support

	Larrar et al. (2006) (n = 53)	Campion et al. (2006) (n = 69)	Thia et al. (2008) (n = 31)	Cambonie et al. (2008) (n = 12)	Martinon-Torres et al. (2008) (n = 12)
Baseline PCO ₂ (mmHg)	62	69	55.8	64	61.6
Baseline RR (breaths/ mn)	61	–	53	61	–
Baseline pH	7.3	7.27	7.3	7.29	–
Baseline HH (beats/mn)	159	–	151	159	–
m-WCAS	–	–	–	5.3	7.7

Initial characteristics of patients

PCO₂ partial pressure of carbon dioxide, RR respiratory rate, HH heart rate, m-WCAS modified Wood's clinical asthma score

airway obstruction (Fauroux et al. 2001; Essouri et al. 2005), but no data has been published for young infants with more distal obstructive airway disease. Recently, Cambonie et al. showed that nCPAP can significantly decrease respiratory effort in 12 infants with severe bronchiolitis (Cambonie et al. 2008). We made similar observations in ten infants with acute bronchiolitis and further demonstrated that nCPAP can adequately decrease oesophageal and diaphragmatic pressure time product (PTP_{es} and PTP_{di}), reflecting diaphragm oxygen consumption and work of breathing (WOB) (Essouri et al. 2011). Although there is no published consensus, all clinical and physiological data allow us to assert that nCPAP is a good respiratory support in infants of less than 1 year old with viral bronchiolitis.

41.1.2 Initiating CPAP

Implementation of CPAP respiratory support requires to answer to the following questions: (1) When CPAP should be initiated? (2) Which devices should be used? (3) In which setting should CPAP be initiated?

The timing of NPPV initiation in patients with neuromuscular disease has been well established in numerous studies (Robert et al. 1993; No authors listed 1999; Finder et al. 2004), but there is no similar data regarding the criteria for CPAP initiation during acute respiratory failure. However, it is certainly easier to define the non-indication for CPAP than to characterise the clinical parameters leading to the decision to initiate CPAP. Nevertheless, criteria used for nCPAP ini-

tiation in published experience of infants bronchiolitis are shown in Table 41.2. Interestingly, authors have quantified the extent of respiratory distress during acute bronchiolitis with the modified Wood's clinical asthma score (m-WCAS) (Table 41.3) (Hollman et al. 1998; Martinon-Torres et al. 2002; Cambonie et al. 2006). Strength of m-WCAS resides in its use in all children, irrespective of the age, and the easiness of the scoring by any health-care providers. In addition, Cambonie showed that m-WCAS efficiently correlates with respiratory effort intensity measured by the oesophageal pressure (P_{es}) swings, PTP_{es}/breath and PTP_{es}/mn. Interestingly, a significant correlation between the decrease in P_{es} swings and use of accessory muscles score is also described (Cambonie et al. 2008). All published data are in agreement with recent experience showing that clinical signs of respiratory distress (increase respiratory rate and high transcutaneous PCO₂) are correlated with an increase in respiratory muscles load and WOB (high oesophageal and diaphragmatic PTP) (Essouri et al. 2011). Based on published experiences, some criteria for the initiation of CPAP during paediatric acute respiratory failure can be suggested: alteration of gas exchange with PCO₂ ≥ 50 mmHg, clinical respiratory distress with m-WCAS > 5, increase in respiratory rate (≥ 2 SD) and bronchiolitis with recurrent apnea. However, CPAP should be contraindicated in the following conditions: cardiac or respiratory arrest, undrained pneumothorax, nonrespiratory organ failure (hemodynamic instability, severe encephalopathy) and inability to protect the upper airway.

Table 41.3 Modified Wood's clinical asthma score

	Score			
	0	0.5	1	2
Cyanosis	SpO ₂ ≥95 % in room air	95 % > SpO ₂ ≥90 % in room air	SpO ₂ ≥90 % with FiO ₂ >0.21	SpO ₂ <90 % with FiO ₂ >0.21
Inspiratory breath sounds	Normal	Slightly unequal	Unequal	Decreased or absent
Accessory muscles use	VAS <5 cm	10 cm > VAS ≥5 cm	15 cm > VAS ≥10 cm	VAS ≥15 cm
Expiratory wheezing	VAS <5 cm	11 cm > VAS ≥5 cm	15 cm > VAS ≥10 cm	VAS ≥15 cm
Cerebral function	Normal	Agitated if disturbed	Depressed or agitated	Coma

SpO₂ pulse oximetry, FiO₂ fraction of inspired oxygen, VAS distance in cm measured by the observer on a 20 cm visual analogue scale

CPAP support requires four components: a ventilator or flow generator, a circuit, a humidifier and an interface. Theoretically, a simple flow generator with an external PEEP can be used to implement CPAP (Beasley and Jones 1981; Soong et al. 1993). Currently, many devices are commercially available, ranging from the simple jet CPAP to polyvalent ventilators used in intensive care unit. The most important parameter is to maintain a stable positive expiratory pressure during the whole respiratory cycle. There is no problem of patient-ventilator synchrony and inspiratory or expiratory trigger as we will see in the NPPV. Cambonie et al. describe that a significant decrease in oesophageal PTP is observed with Infant Flow® (Electro Medical Equipment Ltd, Brighton, United Kingdom) when the level of pressure is achieved (Cambonie et al. 2008). We also describe the same result in decreasing the oesophageal and diaphragmatic PTP with the Babylog 8000™ (Dräger, Lubeck, Germany) (Essouri et al. 2011). Humidification and warming of the gas delivered are critical even for nasal CPAP, especially when fresh gas is used. Most frequently, duration of CPAP support lasts from a few hours to days until respiratory failure resolves. In such circumstances, exposure to cold gas can lead to local inflammation and delayed healing of the respiratory mucosa (Hayes et al. 1995; Randerath et al. 2002). For young infants, the heated humidifier is the best adapted (Jaber et al. 2002; Lellouche et al. 2002). The circuit between the ventilator, or flow

generator, and the interface can be single or double stranded and has to be adapted to the used interface. Prongs and small nasal masks are the most frequently used nCPAP interfaces. The two main systems used in Europe are Infant Flow® (Electro Medical Equipment Ltd, Brighton, United Kingdom) and Fisher & Paykel Healthcare (Auckland, New Zealand). The second one provides prongs available for infants weighing more than 3 kg of body weight. A more recent interface is the helmet with the new “baby body”. The modified helmet that seems to be a suitable device for delivering CPAP is well tolerated without major side effects. However, only a feasibility study on 15 children has been published (Codazzi et al. 2006), and no data are available for infants. Several questions remain pending regarding the helmet system: (1) What is the physiological consequence CO₂ rebreathing? (2) What is the minimal body weight considering that in the smallest, interface overlap may alter thoracic compliance?

As the primary endpoint of the CPAP is to avoid severe respiratory failure leading to invasive ventilation, in patients with an acute respiratory failure, CPAP should be initiated as soon as possible. Thia et al. compared evolution between two groups receiving either early CPAP or delayed CPAP after 12 h of standard therapy. They observed a significant decrease in PCO₂ following early CPAP when compared to delayed CPAP, suggesting that early treatment has prevented the development of additional

airway collapse, slowing up and reversing the natural progression of the disease (Thia et al. 2008). Different situations may arise depending on the delay of admission to a PICU. In the last few years, French emergency transport teams were trained to use nCPAP before transfer to an experienced PICU. Although no international recommendation has been published, it can be anticipated that early CPAP, before and outside the intensive care unit, can prevent further respiratory deterioration. The 2001 International Consensus Conferences on noninvasive positive pressure ventilation in adults ARF have stated that “the optimal location for patients receiving NPPV depends upon the capacity for adequate monitoring, staff skill and experience in explaining the procedure, their knowledge of the equipment used, and awareness of potential complications” (Evans 2001).

41.1.3 Airway Pressure Adjustments During CPAP Therapy

The physiologic data emanating from studies are scarce, and currently level of CPAP is defined empirically determined on the basis of clinical tolerance and clinical response. Shortly, the CPAP level should be set up to the pressure level achieving a decrease in both respiratory muscle load and work of breathing without increasing air leaks. In published experiences of nCPAP for acute viral bronchiolitis, summarised in Table 41.1, level of CPAP was between 5 and 7 cm H₂O. This pressure level was shown to be effective and safe in infants with mild respiratory distress (Courtney et al. 2003; Martinon-Torres et al. 2006; Cambonie et al. 2008; Martinon-Torres et al. 2008). Based on the recent work of Cambonie et al., we actually know that the level of 6 cm H₂O is adapted for infants with acute obstructive airway distress (Cambonie et al. 2008). With this level of CPAP, there is a homogeneous decrease in the values of inspiratory effort of 53 % for Pes swing, 58 % for PTPes/breath and 59 % for PTPes/mn. These data are in agreement with our own in 10 infants with bronchiolitis managed with a mean level of

CPAP of 7 cm H₂O. We observed a significant and homogeneous reduction of oesophageal and diaphragmatic swings from, respectively, 48 and 50 % and from 55 % for oesophageal PTP and 53 % for diaphragmatic PTP (Fig. 41.1). For each infant, we also measured physiological data with high level of CPAP (until 10 cm H₂O) without increase in respiratory effort and in seven infants decrease in the comfort score measured. With low level of CPAP, we observed a decrease in the improvement of oesophageal and diaphragmatic PTP (Essouri et al. 2011). Therefore, based on published clinical experience and physiological data, the recommended level of CPAP for the management of severe acute bronchiolitis is around 7 cm of water.

An additional question is unanswered: Is the level of CPAP support dependant of the age and weight of the patient? The only published data (neonates excluded) are issued from patients with upper airway obstruction. We showed in ten patients that there was no correlation between optimal level of CPAP, defined by the maximum decrease in oesophageal and diaphragmatic PTP and patient age (Essouri et al. 2005).

41.1.4 CPAP Failure Criteria

Incidence of CPAP supports failure, usually defined by the necessity to support respiratory function through invasive ventilation (i.e. orotracheal intubation and mechanical ventilation), has progressively decreased, from 17 to 33 % in the early years of the CPAP therapy for bronchiolitis (Campion et al. 2006; Larrar et al. 2006; Javouhey et al. 2008) to 5 % in the most recent years. Factors associated with the reduction of CPAP failure are now becoming clearer: early CPAP, improvement of interface and health-care provider training in NIV (Essouri et al. 2011).

Despite the recent decrease in failure of CPAP for bronchiolitis, early identification of CPAP failure remains critical as patients requiring invasive ventilatory support have increased morbidity. Some studies have been performed in paediatric patients but are referring to bi-level NPPV (see Sect. 2.2.4). Concerning CPAP

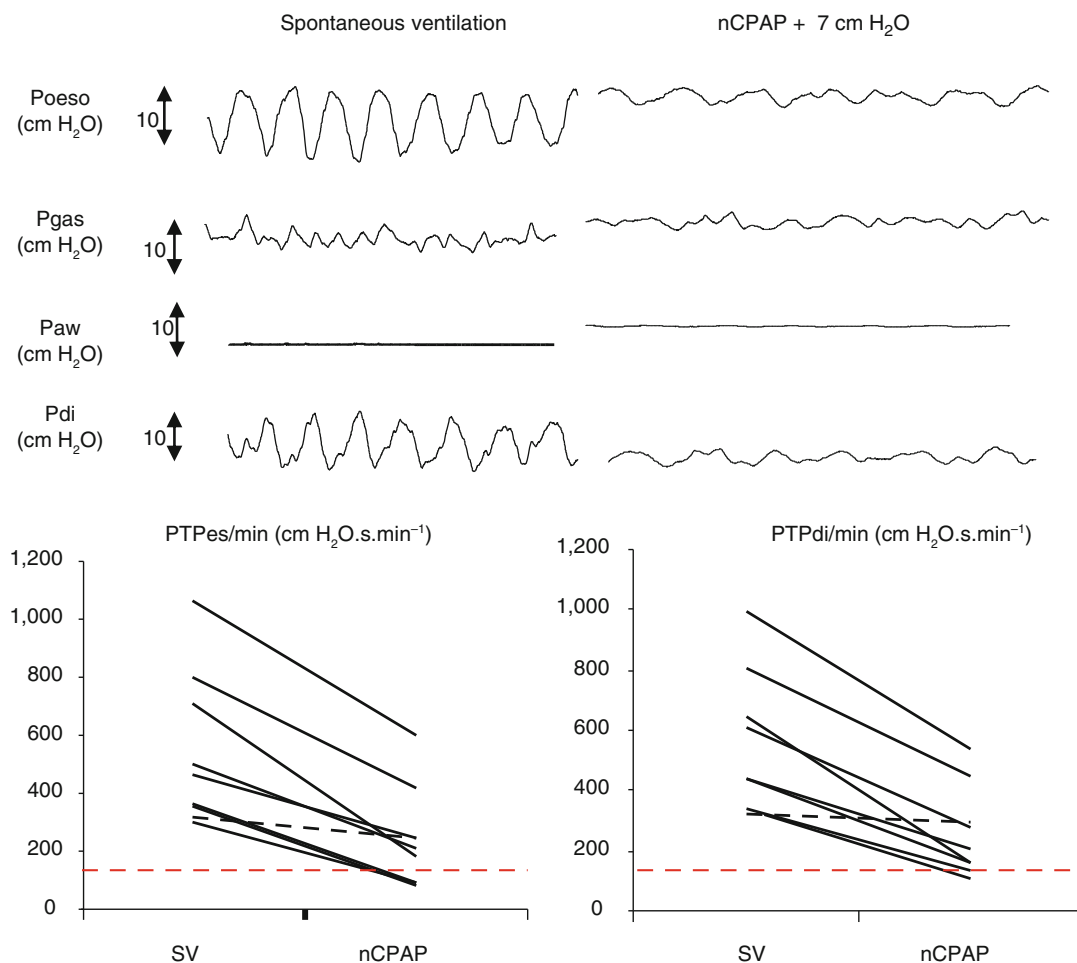


Fig. 41.1 Physiological effect of nasal CPAP support (*nCPAP*) on respiratory effort evaluated by PTPes and PTPdi measured during spontaneous breathing (SB) and nCPAP

support, only retrospective studies are available and concerns acute bronchiolitis (Bernet et al. 2005; Campion et al. 2006; Larrar et al. 2006). A prospective study of NIV (both CPAP and NPPV) in 116 paediatric patients identified three independent risk factors for NIV failure: type 1 acute respiratory failure (defined by Teague (2003)), high PRISM score, and a lower respiratory rate decrease during NIV (Mayordomo-Colunga et al. 2009). However, this study did not look separately to CPAP and NPPV failure. Interestingly, we have reported that high PRISM score during the first 24 h and no and/or a small decrease in PCO₂ during CPAP support were significantly associated with CPAP failure during acute viral bronchiolitis (Larrar et al. 2006). Similar results

were found by Campion et al., who showed additionally apnea and higher PCO₂ as risk factors for CPAP failure (Campion et al. 2006) (Table 41.4).

41.1.5 Undesired Side Effects

Paediatric patients are prone to a wide range of undesired side effects due to physiologic characteristics related to immaturity of the airway protective reflex, high nasal resistance and tendency to mouth breathe (Teague 2003). Frequent side effects are summarised in the Table 41.5. However, most studies involving young children showed an excellent tolerance to nCPAP. Indeed, skin damage (bridge of the nose, nasal mucosa

Table 41.4 Failure of CPAP and NPPV supports

CPAP failure criteria	NPPV failure criteria	
	Before NPPV	During NPPV
Required $\text{FiO}_2 \geq 80\%$	Type 1 ARF	Increase FiO_2 needs
No or small decrease in PCO_2	ARDS	Lower RR decrease
Lower RR decrease	High PRISM score	Lower PCO_2 decrease
Recurrent apnea		
High PRISM score at H24 of PICU stay		

CPAP continuous positive airway pressure, NPPV noninvasive positive pressure ventilation, FiO_2 fraction of inspired oxygen, PCO_2 partial pressure of carbon dioxide, RR respiratory rate, ARF acute respiratory failure, ARDS acute respiratory distress syndrome, PRISM paediatric risk of mortality, PICU paediatric intensive care unit

and upper lip) remains the most frequent complication of CPAP. Fauroux et al. observed that in a population of children with chronic NPPV, skin damage was related to the use of commercial masks (Fauroux et al. 2005). Therefore, reducing the risk of skin damage is among the priority in order to improve tolerance of CPAP. Among the strategy to prevent skin damage, avoiding excessive tight fit is mandatory (Nava et al. 2009). Although frequently mentioned as a complication of CPAP, no pneumothorax was described in the six published clinical studies looking at nCPAP support for acute bronchiolitis (Campion et al. 2006; Larrar et al. 2006; Martinon-Torres et al. 2006; Cambonie et al. 2008; Javouhey et al. 2008; Thia et al. 2008). Agitation and difficulty to adapt to the interface were described but disappeared with the use of oral sedation (30–56 %) (Campion et al. 2006; Thia et al. 2008; Mayordomo-Colunga et al. 2009).

41.1.6 Practical Hints for CPAP Applications

A protocol designed for the medical and nursing staff is required. Clear indications for CPAP initiation and technical hints for how to initiate and maintain CPAP should be established based on the following suggestions (see Fig. 41.2):

Table 41.5 Main side effects of CPAP and practical ways to reduce them

Undesired side effects of CPAP	Ways to reduce
Skin damage	Adapted size, protection by hydrocolloid
Excoriation around the nose	Rotate various types of interfaces
Air leaks	Good position
Eye irritation	Good position
Nasal dryness causing thick secretions	Humidification and reducing airflows if possible
Gastric distension	Gastric tube deflation

- Evaluate indication for CPAP.
- Explain to the parents.
- Start monitoring (pulse oximetry, heart rate, respiratory rate, transcutaneous CO_2 if available).
- Select the adequate interface, hold it in place with the adequate size of cap.
- Set up the ventilator/pressure generator (PEEP 5–7 cm H_2O , minimal flow 12 L/mn).
- Adjust FiO_2 to maintain SpO_2 between 90 and 98 %.
- Perform clinical and gas exchange assessment after 2 h of CPAP.

The success depends of the quality of the health-care training. Regular sessions are required to optimise the success of CPAP implementation.

41.2 Noninvasive Positive Pressure Ventilation

Sandrine Essouri

41.2.1 Indications

During the last decade, NPPV has been increasingly used to provide ventilatory support in various groups of patients with respiratory failure. In adults, recommendations for NPPV in ARF were published (Evans 2001). In paediatrics, no such recommendation exists, although the French Societies of Paediatric Intensive Care and of Pulmonology have recently published a common statement for NPPV support in children with laryngomalacia. Indeed, NPPV support in

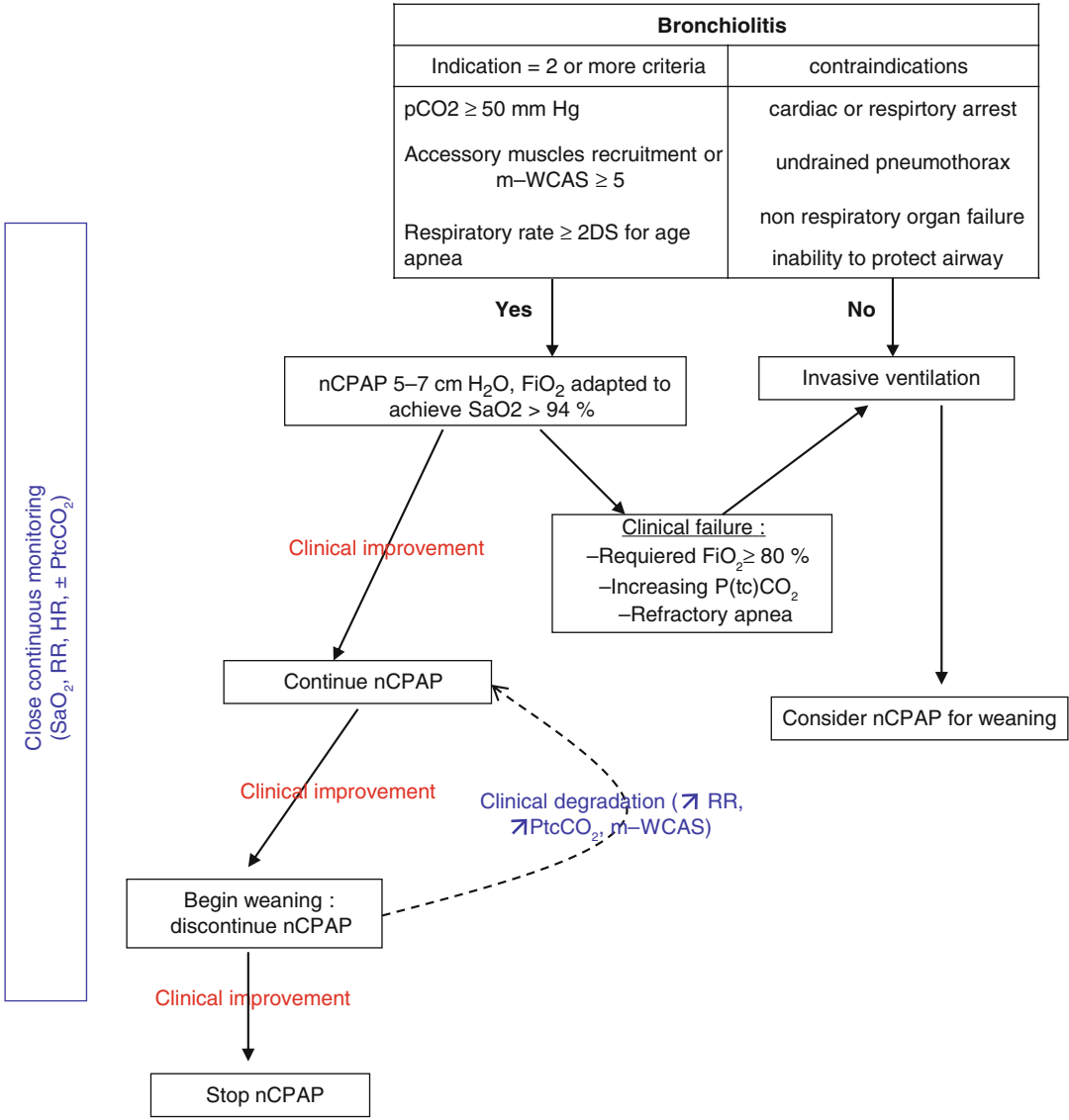


Fig. 41.2 Practical use of nCPAP for severe acute bronchiolitis

children with ARF may provide significant support. Children are at increased risk of respiratory failure due to the relative instability of the developing respiratory system (Hershenson et al. 1990; Devlieger et al. 1991). The functional residual capacity in young infants is close to the total lung capacity because the chest wall is highly compliant (Davis et al. 1988; Papastamelos et al. 1995) and the immature lung has a high elastic recoil (Agostoni 1959). In addition, the diaphragmatic

distribution of muscle fibre type 1 is unfavourable with fewer fatigue-resistant units (Le Souef et al. 1988) making young infants prone to respiratory distress and alveolar hypoventilation. However, little has been published on the physiological response induced by the use of NPPV in ARF. As previously shown, respiratory muscle load can be evaluated using the oesophageal and gastric pressure recorded by a nasogastric tube with two integrated pressure transducers (see Fig. 41.1).

The diaphragmatic PTP and oesophageal PTP are obtained by measuring the area under the diaphragmatic pressure signal and oesophageal pressure signal between the onset of the inspiration, defined as the point at which occurred the deflection on the Pes trace, and the end of the inspiration defined as the peak of Pdi. Analysis of respiratory mechanics in a group of 12 patients with ARF treated with NPPV, showed in all the patients, a decrease in dynamic compliance and an increase in the different components of the work of breathing regardless of the underlying aetiology (Essouri et al. 2008).

Published experience of NPPV support in children with ARF is heterogeneous. Respiratory failure was secondary to a variety of pathology, including severe community-acquired or hospital-acquired pneumonia, post-extubation ARF, status asthmaticus, acute chest syndrome in sickle-cell disease (ACS), chest trauma and acute respiratory distress syndrome (ARDS). In addition patient characteristics, such the age and weight also varied indeed, despite the wide heterogeneity of the studied population, NPPV seemed to be well tolerated, with a low rate of intubation (between 9 and 43 %) (Fortenberry et al. 1995; Padman et al. 1998; Thill et al. 2004; Bernet et al. 2005; Chin et al. 2005; Essouri et al. 2006). However, published data do not suggest that all causes of ARF do well respond to NPPV. In a large cohort of 114 children, ARDS was identified as an independent risk factor of NPPV failure in children (Essouri et al. 2006). This is in agreement with data in adults (Antonelli et al. 2001; Ferrer et al. 2003) and was confirmed in a recent prospective study looking at 116 children with NPPV support for ARF (Mayordomo-Colunga et al. 2009). They found that type 1 ARF (characterised primarily by hypoxaemia with a low arterial PaO_2 and normal to low arterial PaCO_2), and a high PRISM score were independent risk factors for NPPV failure. Therefore, acute hypoxaemic respiratory failure does not seem to be a valid indication for NPPV use. All other causes of ARF seem to respond to NPPV. Current indications for NPPV in children with ARF are summarised in Table 41.6.

Table 41.6 Indications and contraindications of NPPV in acute respiratory failure in children

Indications of NPPV	Contraindications of NPPV
Post-extubation ARF	Cardiac or respiratory arrest
Atelectasis, postoperative diaphragmatic dysfunction	Nonrespiratory organ failure
Community-acquired or health-care associated pneumonia	Severe encephalopathy (e.g. GCS <10)
ARF in immunocompromised patient	Severe upper gastrointestinal bleeding
Acute chest syndrome (sickle-cell disease)	Hemodynamic instability
Status asthmaticus	Facial surgery, trauma or deformity
Left ventricular dysfunction	Fixed obstruction of upper airway
Near drowning	Inability to cooperate/protect the airway
	Inability to clear respiratory secretions
	High risk for aspiration
	No-drained pneumothorax
	Excessive secretions
	Uncooperative or agitated

ARF acute respiratory failure, GCS Glasgow coma score

41.2.2 Initiating Noninvasive Positive Pressure Ventilation

Three parameters should be taken into account for NPPV success: the choice of an adapted interface, the ventilator and the ventilatory mode. A well-fitted comfortable interface is crucial to ensure success of NPPV. Nasal masks have advantages over oronasal masks, such as greater comfort, reduced risk of claustrophobia and better expectoration. However, nasal masks are more prone to air leakage through the mouth and have been associated with a higher rate of initial intolerance during acute applications of NPPV in adults (Kwok et al. 2003). Because children with respiratory failure breathe mostly through the mouth, in order to bypass high nasal resistance, during ARF oronasal interfaces are preferred. In adults with hypoxaemic respiratory failure, the helmet has

been demonstrated to be as efficient as the face mask. Physiological data suggested that, when compared to the face mask use, helmet resulted in greater inspiratory muscle effort. Nonetheless, when both pressures support and PEEP level are increased, inspiratory efforts are similar (Vargas et al. 2009). The place of the helmet interface for NPPV with bi-level pressure support has not been established in paediatric patients. Although, the modified helmet (baby body) interface seems to be suitable for CPAP delivery in children, patient-ventilator asynchrony makes its use for NPPV delivery more hazardous. Published experience of NPPV with helmet interface in children is limited. It has been used in immunocompromised children in a small clinical study with four patients, with age ranging between 9 and 17 years old, showing that the use of the helmet circumvents the disadvantages of the face mask, while maintaining the indications and benefits of a true pressure support ventilation (Piastra et al. 2004). Recently, 26 immunocompromised children with ARDS receiving NPPV with either an oronasal mask ($n=10$) or an helmet ($n=13$) failed to identify any difference between both interfaces (Piastra et al. 2009). In the later study, all children were over 9 years old allowing good patient-ventilator synchrony, even with the helmet interface.

One of the key differences between invasive and NIV are the air leaks. Air leaks cause problems during the different phases of a respiratory cycle. During the initial phase, it causes delayed triggering or missed trigger effort, auto-triggering. Leaks can also decrease rate of inspiratory pressure rise and when they are large enough, delays cycling to the expiration phase in normal and obstructive conditions. Finally, leaks can reduce positive end-expiratory pressure. Ventilators adapted for NPPV are those able to counteract the above-mentioned consequences of air leaks. There are three general classes of ventilator that can be used for NPPV (Chatburn 2009):

1. Home care ventilators, such as piston-driven ventilators (e.g. Lifecare PLV-100, Saime Eole 3.), have been the standard home care ventilator for decades. They are typically used in volume mode, but some of them can be set

to deliver pressure control ventilation. These ventilators are easy to use, offer adequate alarms and can operate on battery power but require an oxygen bleed-in modification to control FiO_2 . The major concern is that they are not designed to compensate for leaks which may cause triggering problems, especially in young children. They are therefore not suited for use in ARF.

2. Devices specially designed for NPPV called “noninvasive ventilators” including: simple noninvasive ventilators, most often used at home in non-acute settings, and advanced NPPV ventilators (e.g. Respironics Vision) which additionally offer control of FiO_2 , graphic monitoring and alarms. The latter are most often used in intensive care units. These ventilators are adapted for use in children.
3. Finally, ICU ventilators which were originally designed to ventilate intubated patients with minimal or no leaks. With the growing use of NPPV, some newer ICU ventilators (e.g. Maquet Servo-i, Dräger Evita 4, Evita XL, Hamilton G5, Viasys Vela) have noninvasive ventilatory modes. When activated, these NPPV modes automate leak compensation and deactivate some nuisance alarms. Although NIV modes can compensate most interference, Vignaux et al., in a study evaluating the performance of NNPPV modes in all current ICU ventilators commonly distributed in Europe, showed that leaks still impair several key functions of ICU ventilators (Vignaux et al. 2007). Altogether, best choices for NPPV support of children with ARF are represented by the ICU ventilators with NIV option or advanced NPPV ventilators if available.

In paediatric ARF, no recommendation regarding the mode of NPPV support is available, but in practice, pressure support ventilation is the mode usually use by most of us. Although, tidal volume (V_t) is more stable in volume control mode with changing lung mechanics, pressure control mode permits a more stable volume delivery with leak and better patient-ventilator synchrony because pressure control allows the

patient to adjust inspiratory flow (Chatburn 2009). Most ventilators suitable for NPPV offer various ventilatory modes, such as CPAP mode, spontaneous, timed and spontaneous/timed operating modes. In the spontaneous mode, the ventilator responds to a threshold level of inspiratory flow that is initiated by the patient's spontaneous respiratory effort. The ventilator then delivers additional gas flow to reach the preset inspiratory positive airway pressure. Exhalation occurs after the inspiratory flow peaks and then decreases to a threshold level. In the timed mode, the ventilator does not trigger in response to flow changes but delivers intermittent positive airway pressure at a set rate. In the spontaneous/timed mode, the flow trigger feature is activated; the ventilator cycles in the timed mode only in the event of prolonged apnea or low minute ventilation. Paediatric patients are most often managed with NPPV in the spontaneous/timed mode. A significant decrease in oesophageal and diaphragmatic PTP was found during spontaneous/timed mode NPPV in 12 children with ARF (Essouri et al. 2008). The high trigger sensitivity of the ICU ventilator allows good patient-ventilator synchrony even for small children.

To date, there is no clear recommendation concerning the humidification during NPPV or CPAP used for ARF in adult and in children. The use of dry gases during nasal CPAP in healthy subjects has been shown to increase nasal resistance (Richards et al. 1996). The nasal resistance is already high in children, and additional increase in resistance should be avoided. Air humidification allows a decrease in flow resistance by decreasing air viscosity coefficient. Heated humidifier should be preferred to heat and moisture exchanger that increase work of breathing and reduce CO₂ elimination during NPPV (Lellouche et al. 2002, 2009).

In conclusion, the most adapted interface for applying NPPV in the acute setting is either the oronasal mask or the helmet for older children and the oronasal mask for smaller children and infants. Indeed, NPPV support requires continuous monitoring in ICU and expertise of trained professionals.

41.2.3 Airway Pressure Settings and Adjustments During NPPV Therapy

Although both inspiratory pressure support and PEEP reduce WOB, physiological mechanisms are different. Pressure support reduces WOB by assisting a greater proportion of transpulmonary pressure during inspiration (Kallet and Luce 2002), whereas PEEP reduces WOB by two other mechanisms. First, PEEP counterbalance intrinsic PEEP (PEEPi), thereby reducing the threshold load to inspiration (Sydow et al. 1995), and second PEEP increase respiratory system compliance, thus reducing the elastic load to inspiration (Katz et al. 1985). Kallet et al. recently examined the physiologic effect of NPPV on WOB, breathing pattern, respiratory system mechanics and hemodynamic function by analysing 41 clinical studies in adults published between 1990 and 2008 (Kallet and Diaz 2009). They found that the average level of inspiratory pressure assistance that maximally reduces WOB and inspiratory effort is 15 cm H₂O with a PEEP level of 5 cm H₂O. In children, the average level of inspiratory pressure over the PEEP is between 8 and 10 cm H₂O, and the average level of PEEP is 6 cm H₂O. In our own experience, these levels of pressure were associated with a significant decrease in oesophageal and diaphragmatic PTP, respectively, -49 and -56 % (Essouri et al. 2008). Moreover, with these levels of pressure, there was a clinical improvement in respiratory rate and a reduction in mean partial pressure in carbon dioxide. These data allow to suggest the following ventilator settings for NPPV support of children with ARF:

- Mode: pressure support or time-cycled PPV
- PEEP: 5 cm H₂O, increase PEEP depending on indication
- Inspiratory pressure support (over PEEP): beginning with 5–6 cm H₂O and increasing by steps of 2 cm H₂O to 8–10 cm H₂O based on clinical efficacy and tolerance
- Trigger: maximum sensitivity (0.3–1 L/mn) without auto-triggering

- Adjust FiO_2
- Active “apnea ventilation parameters” according to the patient age (tidal volume and back up rate)

Nevertheless, establishing NPPV protocol should be encouraged in order to standardise indication and NPPV implementation. A proposed protocol is shown in Fig. 41.3. In practice, a few additional recommendations should be done. It is important to explain the consequences and implementation of NPPV support, to reassure parents and children. When setting up NPPV support, manually hold the mask to familiarise the child with it, then start with low but sufficient parameters (inspiratory pressure, PEEP), secure the mask with the straps and headgear, and finally adjust the pressure support.

41.2.4 NPPV Failure Criteria

Several studies in adults and more recently in paediatrics have shown that NPPV is a safe and effective therapy for patients with ARF of various etiologies (Padman et al. 1998; Essouri et al. 2006; Mayordomo-Colunga et al. 2009). Indeed, NPPV failure should be recognised in order to implement invasive ventilation. In adults, two large multiple-centre studies identifying predictive factors for NPPV failure were published (Antonelli et al. 2001, 2007). However, since cause of ARF in children differs from adults, extrapolation from adults to the paediatric population should be made cautiously. However few paediatric series were published mostly on acute viral bronchiolitis (Essouri et al. 2005; Joshi and Tobias 2007). Bernet et al. (2005) perform a prospective study which identified an $\text{FiO}_2 > 80\%$ one hour after NPPV starts as a predictive factor for NPPV failure with a sensitivity of 56 % and a specificity of 83 %. More recently, Mayordomo-Colunga et al. identified several factors related to NPPV failure (Mayordomo-Colunga et al. 2009) (Table 41.4). Risk for NPPV failure can be divided into risk factors present before NPPV initiation, such as type 1 acute respiratory failure/ARDS and high PRISM score, and risk factors appearing during NPPV, such as lower

respiratory rate decrease at H1 or H2 of NPPV, lower decrease in partial pressure carbon dioxide at H1 or H2 of NPPV, and increased FiO_2 requirement. Patients presenting risk factors for NPPV failure should be closely monitored to detect early signs of failure to either maximise NPPV support or initiate invasive ventilatory support.

41.2.5 Undesired Side Effects

Although NPPV is an efficient and safe therapy for respiratory failure in children, several side effects have been reported. Most of the undesirable effects are minor complications such as eye irritation and skin lesions, but major complications such as gastric distension, gastric perforation, pneumothorax and pneumomediastinum have been reported. Frequency of complication is around 20 % (Gregoretti et al. 2002; Mayordomo-Colunga et al. 2009). Among these, minor complications such as skin lesions are frequent. The most common site of skin damage is the bridge of the nose, the upper lip, the nasal mucosa and, with the helmet, the axillae. This complication is associated with the use of commercial masks (Fauroux et al. 2005) and is directly related to NPPV duration (Mayordomo-Colunga et al. 2009). Skin complications can be prevented and managed as summarised in Table 41.7. Gastric complications were described essentially in neonates (Garland et al. 1985) and can be avoided by gastric decompression with an nasogastric tube. Pneumothorax is an infrequent complication of NPPV (<2 %) (Mayordomo-Colunga et al. 2009). Intolerance of the interface and agitation can be a problem and sometimes, sedation at least during the initiation phase of NPPV is necessary to allow adaptation of the patient.

41.2.6 Conclusion

NPPV support in children is recognised as a major supportive therapy for children with respiratory failure. NPPV should be considered as a precocious option before end stage of ARF to

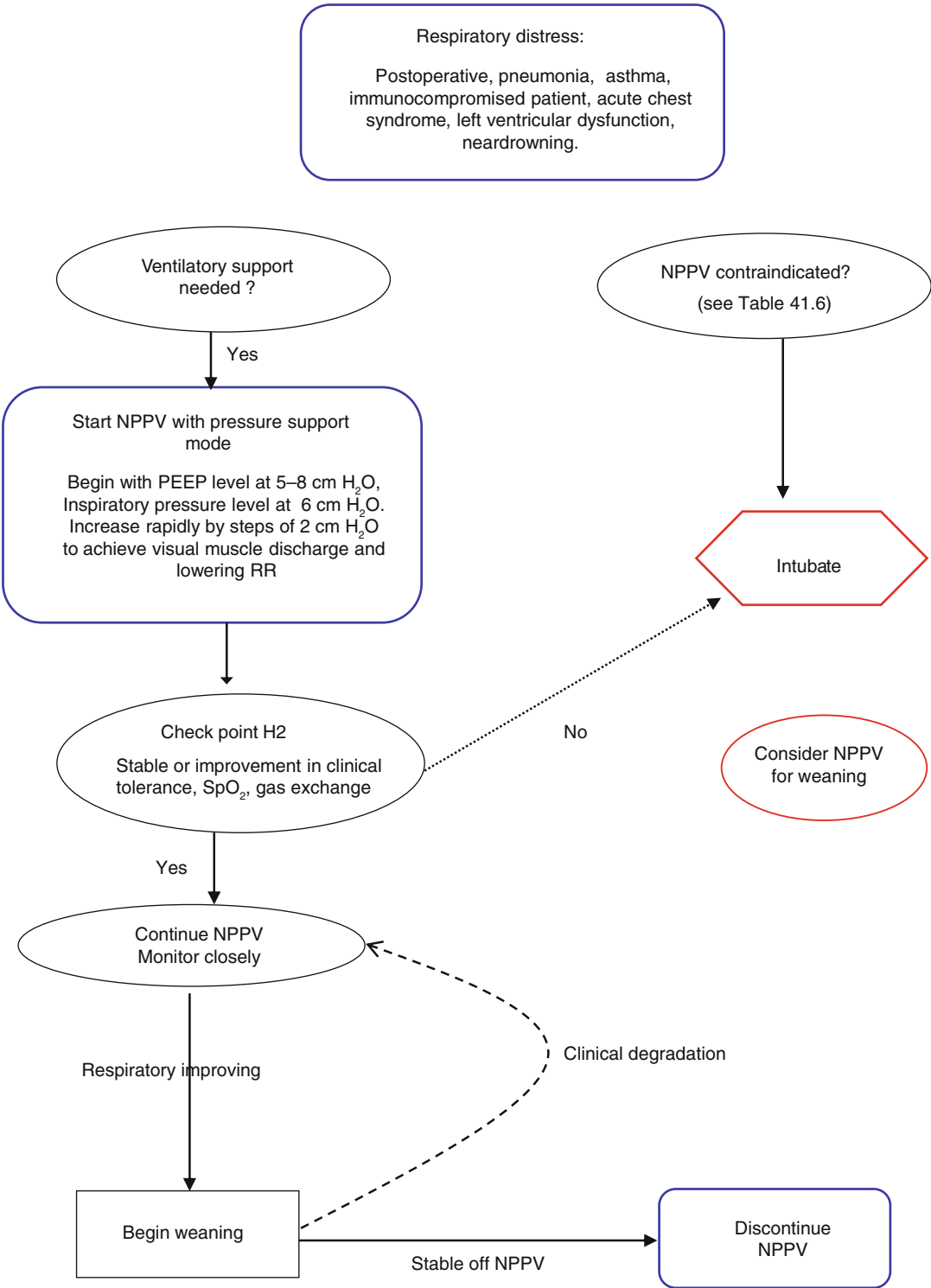


Fig. 41.3 Algorithm illustrating the principles of practical application of NPPV in paediatrics

Table 41.7 Ways to limit skin damage

Steps to avoid skin damage
Choose an adapted interface
Avoid excessively tight fit
Regular switch between various interface
Skin pads to protect common sites of damage
Preferring short periods of NPPV (2–3 h) repeated than longer sessions

NPPV noninvasive positive pressure ventilation

prevent further deterioration and avoid invasive ventilation. However, in paediatric, physiological and epidemiologic data are still missing. Knowledge of clinical indication, implementation, as well as repetitive training of all health-care providers are essential for NIV success.

Essentials to Remember

- NPPV is a major support therapy in management of acute respiratory failure in children and despite the lack of randomized control studies, numerous studies confirm its efficacy and safety.
- Physiologic studies describe physiological efficiency of NPPV support in infants and children with various etiology of respiratory failure.
- Nasal CPAP has become a successful respiratory treatment strategy in severe bronchiolitis and allows to avoid invasive ventilator in most of cases.
- Predictive factors of NPPV failure have been identified and a good knowledge of indications and contraindications is essential.
- To perform NPPV in children, a specific material is needed from the interface to the ventilator. The choice of the material is major to allow a good patient tolerance and to optimize patient-ventilator synchrony.
- NPPV should be performed by an experienced team and the training of health team is essential.

41.3 Adjunctive Therapies During CPAP or NIPPV

Federico Martinon-Torres

41.3.1 Noninvasive Ventilation with Helium-Oxygen Mixture

Educational Aims

- To describe the fundamentals of helium-oxygen utility in the NIV of children
- To provide a comprehensive review of the clinical experience on the use of NIV with helium-oxygen in children
- To provide a thorough review of the practical issues of NIV with helium-oxygen
- To establish precise indications of NIV with helium-oxygen in children
- To detail potential side effects and drawbacks of adjunctive use of helium-oxygen during NIV

41.3.2 Use of Helium-Oxygen Mixtures

Children receiving NIV may simultaneously require supplementary techniques either at the onset of treatment or throughout the progression of their pathology. These techniques may be complementary to NIV and may even enable synergistic effects. One of these applications is its use in combination with helium.

Most existing literature on NIV in combination with helium-oxygen focuses on use in adults, basically for treatment of acute exacerbations of chronic obstructive airways disease. This chapter reviews and summarises the theoretical basis, existing clinical evidence and practical aspects of the use of NIV with helium-oxygen in children

41.3.2.1 Properties of Heliox

Helium was first introduced into the medical practice in the 1930s by Barach, who showed that when it was combined with oxygen, the resulting mixture (which he dubbed “heliox”) improved

airflow in patients with obstructive laryngeal, tracheal or lower airway lesions. Since then, studies on the paediatric use of heliox have demonstrated its utility and efficacy for treatment of various conditions, including upper airway obstruction caused by diverse pathologies, as well as asthma and acute bronchiolitis.

Helium, a noble gas, is inert, colourless and odourless and has very low density. If the nitrogen in inspired air (composed of 78 % N₂ and 22 % O₂) is replaced with helium—which is seven times less dense—a mixture (78 % He and 22 % O₂) is obtained which is three times less dense than normal air. The therapeutic utility of heliox mainly lies in this significant difference in density: when a patient breathes heliox instead of air-oxygen, airway resistance to gas flow is reduced leading to a reduction in respiratory work. Furthermore, heliox also improves gas exchange, above all in alveolar ventilation: in small airways, where elimination of CO₂ is facilitated by diffusion, this diffuses four to five times faster in heliox than in air-oxygen mixture.

41.3.2.2 Clinical Applications of Heliox

As an inert mixture, heliox lacks any intrinsic therapeutic effects. However, it can act as a “therapeutic bridge” maintaining the patient in improved conditions, delaying onset of muscle fatigue and respiratory failure, and obviating the use of more aggressive treatments, until either other therapies can be administered or the patient’s condition spontaneously resolves itself. Furthermore, this lack of any potential biological interaction provides an excellent safety profile for its clinical use, being a therapy without inherent risks: using heliox does not mean taking any biological risk for our patient.

Heliox is most effective at the highest possible concentrations of helium (typically, 60–80 %); nevertheless there may be beneficial effects at much lower concentrations, though with proportionately lower effectiveness. Through its physical properties, the main clinical uses of heliox predominantly relate to obstructive respiratory problems, those that pathophysiologically have both raised airway resistance and increased respiratory work, and also where alveolar ventilation is compromised to a greater or lesser

Table 41.8 Main uses of heliox in children

A. Obstruction mainly of the upper airway
A.1. Infectious aetiology (e.g. laryngitis, epiglottitis, tracheitis)
A.2. Inflammatory aetiology
1. Post-extubation subglottic oedema
2. Post-radiotherapy oedema
3. Angioedema
4. Oedema through inhaled injury
5. Recurrent or spasmodic croup
A.3. Mechanical aetiology
1. Foreign body
2. Vocal cord paralysis
3. Subglottic stenosis
A.4. Laryngotracheomalacia
A.5. Neoplastic aetiology
1. Laryngeal or tracheal growths
2. Extrinsic compression of the larynx, trachea or bronchi
B. Obstruction mainly of the lower airways
B.1. Acute asthmatic crisis
B.2. Bronchiolitis
B.3. Bronchial hyperreactivity
B.4. Neonatal respiratory distress syndrome
B.5. Bronchopulmonary dysplasia
C. Driving gas for drug nebulisation
D. Fibre-optic bronchoscopy and/or instrumental manipulation of the airway
E. Other indications
E.1. Hyperammonaemia
E.2. Pneumothorax

In upper airway obstruction heliox has shown the greatest efficacy and has the most evidence. Use in illness involving mainly the lower airways is more controversial

extent. Table 41.8 summarises the main paediatric clinical areas for the use of heliox. Usual practice, following the majority of existing studies of heliox use in children, is in those breathing spontaneously or, if in intubated patients, by adaptation of conventional mechanical ventilation systems.

41.3.2.2.1 Heliox Therapy in the Spontaneously Breathing Infant

For patients with spontaneous breathing, the preferred method is via non-rebreathing mask with reservoir and unidirectional low-pressure valves at flows of 10–15 L/min. If required, supplementary oxygen can be delivered through nasal

cannulae, but at the lowest flow possible (always <2 L/min), since a higher flow could excessively reduce the helium concentration. Warming and humidification of heliox, which is especially important for very small children, can readily be achieved by modifying standard equipment used for air-oxygen mixtures. Oxygen hoods or tents are not ideally suited to heliox therapy since mixture with room air is greater, with the helium (less dense) going to the top, and the air (more dense) going to the bottom, close to the patient's airway. Simple face masks or nasal cannulae may be amenable to heliox therapy; however, they tend to cause dilution of the heliox flow with external air, thereby markedly reducing the chances of a successful treatment.

41.3.2.2.2 Heliox as Nebulisation Source

A further application, for which significant evidence exists in both children and adults, is to use heliox to nebulise medicines. For this use gas flow is usually increased by 20–25 %, providing that minimum flow is not below 15 lpm. Note that the nebulisation time of any particular volume of solution is much longer than with air or oxygen at a similar flow. To obtain the maximum benefits, a nebulisation system with reservoir (like the non-rebreathing reservoir face mask with a “Y” piece) should be guaranteed, ensuring that patient's minute volume demands are covered with heliox. Alternatively, an ultrasonic nebuliser can be used, intercalated in the heliox flow to the patient.

41.3.2.2.3 Heliox Therapy in the Intubated Child

When used invasively, the method depends upon the type of respirator. Heliox is usually introduced via the pressurised air input of the respirator; however, given its physical properties, it can interfere with a wide range of key functions (volume settings, levels of FiO_2 , trigger sensitivities, flow rates, etc.). Therefore it is necessary to check before use that the ventilator is compatible with heliox and to consider specific correction factors. In general, the safest form of patient ventilation with heliox is to use a pressure-controlled ventilatory mode using pressure goals as a guide (see references for details). Presently, there are

available ventilators specifically designed—and FDA cleared—to be used with helium-oxygen mixtures, although they are not widely distributed yet. Heliox has also been used with other invasive ventilatory modes such as high-frequency jet, high-frequency percussive ventilation, and high-frequency oscillatory ventilation.

41.3.2.3 Rationale for Using Heliox in Noninvasive Ventilation and Clinical Experience

Based on the studies published by the Swiss group, Jolliet and colleagues, at the end of the 1990s in adults, interest began and increased in the combination of NIV and heliox in the treatment of acute exacerbations in patients with chronic pulmonary disease, showing even its efficiency. The use of NIV with heliox in place of air-oxygen occurred for the first time (successfully) in children in the mid 1970s in weaning off small children from mechanical ventilation following cardiac surgery. However, this practice was not repeated (as few used NIV in children at that time) and there are no earlier publications on NIV with heliox in children before those of our own group, on use in young infants with refractory acute bronchiolitis.

Experimental models and clinical data on adults both demonstrate that at a given target pressure, heliox provides greater minute volumes—and therefore, better alveolar ventilation—than air-oxygen mixtures. Increasing the expiratory flow reduces air trapping and generation of auto-PEEP, thereby improving lung compliance, restoring the mechanical advantage to inspiration, and decreasing work of breathing. This in turn expands the tidal volume generated per cm H_2O of pressure used. Moreover, NIV with heliox improves the patient's elimination of CO_2 and reduces their sensations of dyspnea.

Heliox has complementary effects when used with NIV; indeed, the combination of heliox and NIV can even be considered synergistic. As positive pressure, NIV can help reduce the load on respiratory muscles, prevent or correct atelectasis, prevent airway collapse and promote and facilitate distribution of heliox throughout obstructed airways. Heliox can further reduce

work of breathing and improve CO₂ elimination. It can also provide higher expiratory flow than air-oxygen mixtures at the same pressure, which in turn can help improve passive expiratory lung mechanics, reducing the risk of barotrauma by gas trapping and thereby limiting any deleterious side effects from CPAP in obstructed airways.

Application of continuous positive pressure can lower the patient's FiO₂ requirements, enabling them to be treated with a higher concentration of helium, and, consequently, increasing the likelihood of treatment success. The reduction in the oxygen requirements further protects the lung.

Hypoxia secondary to development of atelectasis has been described in patients treated with heliox. Neonates and small infants are at especially high risk for this complication. However, this potentially serious side effect—although anecdotally reported and debatably related to heliox—can easily be prevented through concomitant use of CPAP.

Given that heliox can reduce the pressure gradient required to maintain a given flow, less pressure can be used to obtain the target tidal and minute volumes, which in turn diminishes peak pressures and minimises the risk of barotrauma or volutrauma. In other words, by substituting air-oxygen for heliox, NIV may be performed in a more lung-protective fashion: for a given target pH/CO₂ level, lower pressure swings and even lower volumes will be required.

Lastly, heliox delivered by NIV can delay or even obviate endotracheal intubation of the patient and subsequent invasive mechanical ventilation, each of which carries its respective complications. Although endotracheal intubation is the preferred method for airway isolation, it can produce local inflammation, ischaemia of the mucosa, subglottic oedema and/or stenosis. Likewise, invasive positive pressure ventilation can cause lung damage by altering lung mechanics, specifically, barotrauma, volutrauma, atelectrauma and biotrauma.

Based on the experience of the author's unit, heliox in combination with nCPAP is a safe and effective treatment in unresponsive severe acute bronchiolitis as measured clinically or by tcPCO₂

and by satO₂ values. Furthermore, nCPAP with heliox in place of an air-oxygen mixture (AO-nCPAP) is clearly more efficacious, as shown by approximately twice the level of improvement in clinical scores and tcPCO₂ levels after 30 min of therapy. Between 1999 and 2010, only 1 (0.28 %) of 352 patients admitted to our unit with moderate to severe acute bronchiolitis and managed according to our protocol—centred in the use of heliox alone or in combination with NIV—has needed intubation and mechanical ventilation (95 % exact CI: 0.01–1.12 %). Even though this is a single-centre experience and that there may be influencing factors other than heliox and nCPAP treatment in intubation practices (aetiology, admission-discharge criteria, RSV season...), such low incidence is in stark contrast to the levels noted in a literature review suggesting that 25–60 % of infants with bronchiolitis admitted to a PICU may need intubation and ventilatory support. Importantly, in our experience there were no adverse effects related to heliox, and the technique used was tolerated well in all of the patients.

41.3.2.4 Indications of Noninvasive Ventilation with Heliox in Paediatric Patients

No well-established indications of noninvasive ventilation with heliox in children exist. The author of this chapter has compiled a list of potential indications of heliox used with NIV for paediatric patients, based on the physical properties of heliox, published data from experimental reports and clinical studies on adult patients, as well as—and mainly—his personal accumulated and reported experience. These comprise (Table 41.9):

1. *Children already receiving heliox therapy that are not achieving adequate levels of oxygenation.* The positive pressure will enhance alveolar recruitment/oxygenation, allowing us to reduce FiO₂ (and thus to increase FiHe).
2. *Children already on noninvasive ventilation with inadequate ventilation* according to pH/pCO₂ levels, dyspnea or clinical score. The effect of heliox on alveolar ventilation through higher expiratory flows but also over CO₂ may

resolve the situation without further increase in the NIV parameters.

One further indication, at least from the theoretical perspective, would be in those children receiving NIV whose underlying pathology or illness requires protective ventilatory strategy (i.e. the lowest possible pressure-volume swing (amplitude/IPAP-EPAP) for achieving a target pH/CO₂ level). From the practical point of view,

infants with severe unresponsive bronchiolitis and children with status asthmaticus are the most frequent clinical indications of noninvasive ventilation with heliox.

41.3.2.5 Protocol for Using Heliox with Noninvasive Ventilation

41.3.2.5.1 Equipment Designed for Heliox Delivery

Currently, there are few commercially available ventilators designed for heliox delivery: Aptaer[®] Heliox Delivery System (GE Healthcare), Inspiration[®] (Event Medical Ltd.), Avea[®] (Vyasis Healthcare) and Hamilton G5[®] (Hamilton Medical). The main characteristics of these machines are summarised in Table 41.10. They remain limited in distribution and use; indeed, none of these devices have appeared in any of the few works on paediatric patients published to date. The Aptaer[®] features inspiratory and expiratory triggers, enabling use of pressure support with heliox. The Inspiration[®] is a conventional ventilator that includes an option for NIV delivery of heliox. The Avea[®] offers all the standard modes used for invasive ventilation, plus the option for invasive or noninvasive ventilation with heliox. Currently most of last generation commercially available ventilators include an optional module to allow the use of heliox without interference with the device function as the Hamilton G5[®]. They remain however limited in distribution and use, and there is no published study using these devices.

Table 41.9 Indications of noninvasive ventilation with helium-oxygen instead of air-oxygen

1. Children <i>already receiving heliox therapy</i> ^a with inadequate oxygenation:
Not meeting their oxygenation goals-requirements
Whose FiO ₂ requirement is either >0.40 or increasing
2. Children <i>already receiving NIV</i> with inadequate ventilation:
Ventilation level achieved is inadequate according to pH/pCO ₂
Require high or increasing pressure levels (PIP/IPAP)
Show insufficient improvement (or worsening) in dyspnea
Show insufficient improvement (or worsening) in clinical respiratory score
3. Children receiving NIV whose underlying pathology or illness <i>requires protective ventilatory strategy</i> (i.e. the lowest possible pressure-volume swing (amplitude/IPAP-EPAP) for achieving a target pH/CO ₂ level)

^aHeliox therapy defined as helium-oxygen mixture (60–80 % helium proportion) administered to a spontaneously breathing child through non-rebreathing reservoir face-mask with adequate heliox flow (usually about 10 lpm)

Table 41.10 Noninvasive ventilation with heliox. Main features of the commercially available ventilators designed for noninvasive delivery of heliox with positive pressure

Model	Aptaer [®]	Avea [®]	Event [®]	Hamilton G5 [®]
Distributor	Datex Ohmeda	Vyasis Healthcare	Event Inspiration LTD	Hamilton Medical
Adjustable FiO ₂	No	Yes	Yes	Yes
Adjustable PEEP	No	Yes	Yes	Yes
Pressure support	Yes	Yes	Yes	Yes
Paediatric model	No	Yes	Yes	Yes
Standard ventilation modes	No	Yes	Yes	Yes
Heliox consumption	Low	Medium	Medium	High
Difficulty for portable use	Medium	High	High	High
Price	Low	High	High	High

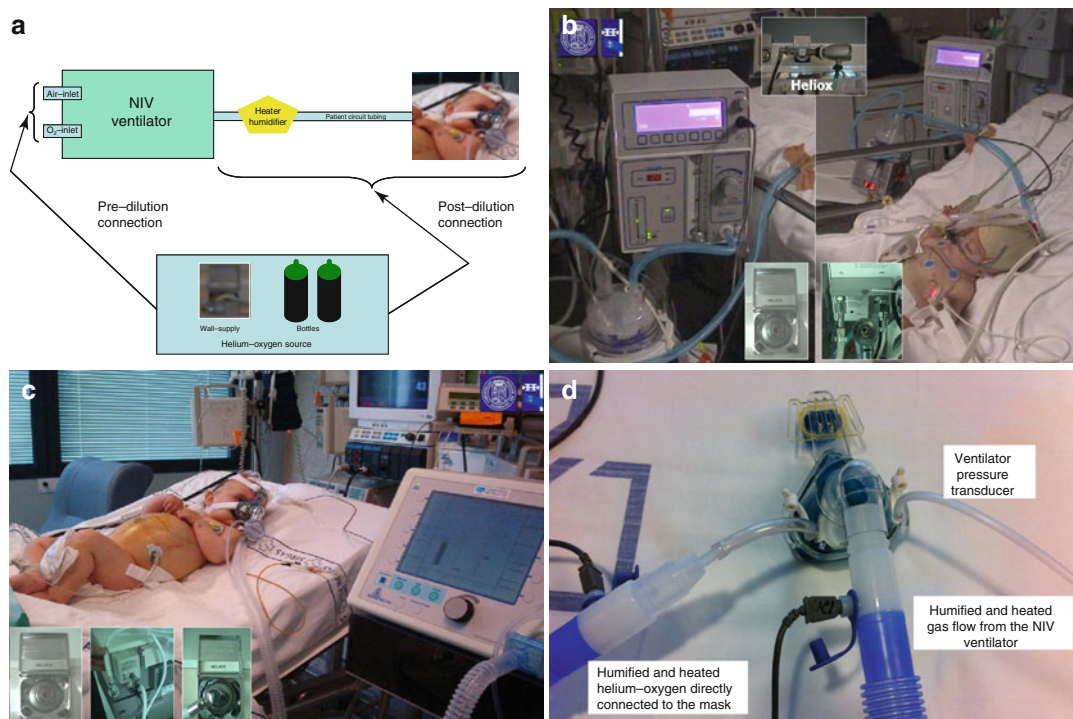


Fig. 41.4 Modes of adaptation of standard NIV equipment for delivery of heliox (a). Examples with Infant Flow[®] (EME) pre-dilutional connection (b), Vision[®]

(Respironics) pre-dilutional connection (c) and Vision[®] (Respironics) post-dilutional connection (d) are provided. See text for further details

41.3.2.5.2 Equipment Adapted for Heliox Delivery

Heliox can be safely delivered by modifying standard NIV ventilators according to literature guidelines. However, as with use of any equipment beyond its manufacturer's indications, extreme caution must be applied when using this approach. Hospital staff must have technical expertise in both the ventilator and in heliox therapy to minimise any potential risks in this method. In these cases we should consider:

1. When heliox is used with NIV, the average flow and volume readings are not reliable, unless an external pneumotachograph (which is not influenced by gas density) is used. Hence, ventilation should be programmed and controlled as a function of the programmed pressures (which are not affected by heliox) and the resulting blood gas values (arterial O₂ saturation and CO₂ levels).
2. NIV with heliox instead of air-oxygen mixtures generates greater inspiratory and

expiratory flows at the same pressure and provides far superior CO₂ diffusion. In terms of protecting the patient's lungs, this implies that the pressure gradient required to reach a given target CO₂ level will be lower with heliox than with an air-oxygen mixture.

3. If pure helium is used—which is generally not recommended and is prohibited by legislation on therapeutic gases in most European countries—then the patient must be continuously monitored by oximetry to prevent hypoxic conditions. Nonetheless, the safest and most practical clinical option is to use helium-oxygen mixtures at predetermined concentrations (typically, 80:20 or 70:30) and then add any required supplemental oxygen according to the patient's needs.

There are two ways of adapting standard NIV equipment for delivery of heliox: pre-dilution connection and post-dilution connection (Fig. 41.4).

41.3.2.5.2.1 Pre-dilution Connection

In this approach heliox is directly connected to the ventilator through a pressurised gas inlet or a blender. It can be employed with the BiPAP Vision® (Respironics) and the Infant Flow, Infant Flow Advance and SiPAP® (EME/Viasys) systems (Fig. 41.4). The helium or heliox source is connected to the ventilator's air inlet (probably the best option) or oxygen inlet. In the former case, the FiO_2 is regulated using the ventilator's FiO_2 control; whereas in the latter case, the FiO_2 control is set to 1.0 to ensure that only heliox is being delivered. If supplementary oxygen is required, it can be added through a T-piece attached to the respiratory circuit. Alternatively, an oxygen blender can be attached to the ventilator's air inlet or oxygen inlet, so that helium and oxygen can be added simultaneously before entering the ventilator.

For cases in which the gas flow is directly regulated (e.g. in the Infant Flow® system), the following factors are used to convert flow metre readings from air-oxygen values to heliox values: for 80 % He and 20 % O_2 , multiply by 2.1; for 70 % He and 30 % O_2 , multiply by 1.7; and for 60 % He and 40 % O_2 , multiply by 1.4. These conversions enable determination of the real amount of heliox required to maintain the target pressure. If heliox is introduced through the air inlet, then the automatic limits of the alarm should be adjusted by first temporarily setting the FiO_2 control to the same percentage as the oxygen in the heliox used and then resetting it to 0.21. This aim of this technique is to avoid false alarms caused by discrepancy between the concentration set on the oxygen blender and the concentration detected by the oximeter (whose minimum value is the percentage of oxygen in the heliox introduced at the air inlet).

NIV delivery of heliox using the BiPAP Vision® ventilator has been validated in an experimental model. However, if this device is used, the initial leakage test of the expiratory valve should not be performed; paradoxically, this will provide better functioning of the ventilator, including greater accuracy of the trigger. Using this method with the FiO_2 set at 1.0 enables safe and accurate administration of helium at concentrations higher than 60 %.

The NIV ventilators best suited to modification for heliox delivery (i.e. those for which heliox causes the least interference in functioning, including in measurements) comprise, in decreasing order of preference: Servo 300®, Galileo®, Galileo Gold® and Veolar FT®. For volume-controlled ventilation (VCV), there are specific correction factors for tidal volume and FiO_2 to be used with the most popular NIV ventilators (see References).

41.3.2.5.2.2 Post-dilution Connection

In this method, the heliox is introduced directly into the respiratory circuit tubing, after the ventilator and ideally, as close to the patient (interface) end as possible. In this set-up, the concentration of helium that the patient receives is primarily dictated by the flow of helium used. Thus, it requires external oximetry to guarantee adequate FiO_2 delivery. Furthermore, since the parameter values registered by the ventilator are not reliable, external pneumotachography is also needed. This set-up is an option in some ventilators (e.g. BiPAP Vision®), whereas it is the only option in others, which generate pressure by drawing in ambient air (e.g. BiPAP S/T-D30, Knightstar 335 [Mallinckrodt], Quantum PSV [Respironics] and Sullivan VPAP II ST [ResMed]). Analogously to the case in standard NIV of trying to increase the FiO_2 by introducing oxygen in the circuit or interface, this approach is limited by the fact that the operator cannot determine exactly how much helium is being introduced into the circuit (and therefore, delivered to the patient), which carries a risk of affecting ventilator function. Nonetheless, it has been validated experimentally. Using any of the aforementioned ventilators with heliox (80 % He and 20 % O_2) flows of 18 L/min ensures delivery to the patient of helium at concentrations higher than 60 %. Furthermore, at this flow rate, heliox only causes minimal interference (BiPAP S/T-D30 and the Quantum) with ventilator function or does not interfere at all (Knightstar, Sullivan and BiPAP Vision), nor does it alter the programmed inspiratory or expiratory pressures in any of these models. Logically, with this heliox delivery approach, the final concentration of helium delivered to

the patient is influenced by the tidal volume obtained: higher inspiratory pressure and greater tidal volume at a constant heliox flow correlate with a lower concentration of helium administered to the patient.

Also recently, helmet-delivered heliox CPAP has been successfully applied in the bronchiolitis setting. This method might simplify the technique. Similarly, we have adapted the boussignac cpap system (Vygon®) for heliox-nCPAP delivery through nasopharyngeal tube with preliminary unpublished but positive results.

41.3.2.5.2.3 Heliox with High Flow

Nasal Cannula

Another intermediate option between plain heliox therapy and NIV with heliox could be heliox therapy with high flow nasal cannula. The main advantage would be the simplicity of this kind of interphase, facilitating its use out of the critical care setting.

The settings will vary depending on the device used. There is an FDA cleared high flow heliox humidified device (Precision Flow® Heliox, Vapotherm). It is specifically calibrated and approved for heliox delivery. Flow can be programmed 1–40 liters per minute, oxygen concentration is adjustable (21–100 %) and heliox supply must be 80/20. In our unit we have developed a specific protocol for the use of heliox with the Optiflow® (Fisher & Paykel) high-flow device. We start with a flow of 8 lpm of HELIOX 70/30 and we increase it gradually according to patients' tolerance and needs, up to the maximum allowed flow for the size of cannula applied.

41.3.2.6 Side Effects and Drawbacks

41.3.2.6.1 Side Effects

Although heliox is inert (nontoxic), when used with NIV it may lead to certain side effects, namely:

41.3.2.6.1.1 Hypoxaemia

The primary side effect is insufficient oxygenation, since this treatment implies use of the lowest FiO_2 possible to maximise the positive effects of helium. Hence, strongly hypoxaemic patients, who are characterised by high oxygen requirements, cannot be treated with heliox (at least not

at any therapeutically significant concentration of helium). Hypoxaemia can also be caused by inadvertent use of a hypoxic mixture ($\text{FiO}_2 < 21\%$) in cases in which the helium and oxygen are mixed manually. This can be avoided by using tanks of pre-mixed heliox at known concentrations or by employing continuous oximetric monitoring (with an alarm) of the mixture delivered to the patient.

41.3.2.6.1.2 Hypothermia

One of the most therapeutically important physical properties of heliox is its high thermal conductivity (six to seven times that of air); hence, prolonged heliox treatment at temperatures under 36°C carries a risk of hypothermia. Neonates and small infants are at the highest risk for this side effect, which can be prevented by ensuring proper warming and humidification of the heliox and by carefully monitoring the patient's body temperature.

41.3.2.6.2 Drawbacks

41.3.2.6.2.1 Cost

There have not been any studies on the cost-effectiveness of NIV heliox treatment. Compared to other gases, heliox is much more expensive: two to three times as much as air and eight to ten times as much as oxygen. Using non-NIV-specific devices for delivery of heliox can lead to increased costs due to internal gas consumption, leakage compensation and/or excessive internal leaks. However, NIV-specific ventilators also have their respective drawbacks, which vary according to model.

41.3.2.6.2.2 Technical Difficulties

The physical properties of heliox—above all, its low density—can interfere with fundamental ventilator operation, especially recording of FiO_2 volumes, as well as trigger functioning, flow measurements and the automatic leakage compensation featured on some models. These technical difficulties vary with the ventilator used and are primarily dictated by the type of valves and pneumotachograph used. In any case, pressure transducers are generally not affected by heliox; hence, treatment should be adjusted according to the programmed pressures.

Future Perspectives

Using heliox with NIV is a promising therapeutic option for children with various respiratory pathologies that do not respond to conventional treatment. According to the author's experience, heliox in combination with CPAP is a safe and effective tool to be considered for the management of infants with severe acute bronchiolitis. However, this technique must be further evaluated in this and other settings, in both experimental and clinical studies. NIV with heliox indications and treatment guidelines (ideal initial and maintenance settings, duration of treatment) must be more clearly established. Furthermore, NIV with heliox theoretically embodies a new strategy for lung treatment and protection, and studies exploring this possibility should be warranted.

Essentials to Remember

- Heliox is complementary to NIV, and together, they may even have synergistic effects.
- There is only a small body of literature on heliox in paediatric NIV—focusing on treatment of severe acute bronchiolitis patients that cannot be treated with standard therapies—but the results are positive.
- Heliox and NIV may provide time for other therapeutic agents to work or for the disease to resolve naturally and might help to avoid more aggressive intervention, such as endotracheal intubation and invasive mechanical ventilation.
- The ideal ventilators for heliox delivery are devices which are specifically designed for this task.
- Alternatively, other ventilators can be modified to administer heliox in NIV, although these must be used with extra precautions.

- Theoretically, NIV with heliox embodies a new strategy for lung treatment and protection.
- The inert nature of helium adds no biological risk to NIV performance.

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Adjunctive Therapies During CPAP or NIPPV

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Part XV

Practical Evidence-Based and Goal-Directed Approach to Conventional Mechanical Ventilation

Peter A. Dargaville and Martin Keszler

Educational Aims

This chapter aims to give an understanding of:

- The clinical situations in which ventilation is applied in the newborn
- The approach to initiation of ventilation, including choice of mode of ventilation and first settings
- The physiological considerations and clinical evidence for adjustment of ventilator settings
- The rationale for target ranges for tidal volume, oxygen saturation and carbon dioxide

different situations in which ventilation is applied to the newborn infant is extremely broad, with in each case different pathophysiological disturbances and often the need to use a specific approach to apply ventilation optimally. Table 42.1 provides a list of the more common situations in which conventional ventilation is used in the neonate and includes some considerations regarding ventilator settings for each situation. For each situation, a suggested mode of ventilation is indicated, along with target ranges for positive end-expiratory pressure (PEEP) and tidal volume (V_T). Further discussion of the physiological rationale and available evidence for ventilator settings is set out below.

42.1 Introduction

Success in providing respiratory support to the neonate requires a clear understanding of the context in which it is being applied. Perhaps more than for any other age group, the array of

42.2 Choosing the Ventilator Mode

To a significant degree, the clinician's choice of ventilator modes is limited by the equipment available in his or her NICU. Although most modern ventilators are capable of providing the basic modes of synchronised (patient-triggered) ventilation, there are a variety of hybrid modes or combinations that may be unique to each manufacturer and device. For example, some ventilators make possible the combination of synchronised intermittent mandatory ventilation (SIMV) and pressure support ventilation (PSV), and other ventilators employ PSV as a stand-alone mode with a backup rate, similar to assist/control (AC) but flow rather than time cycled. PSV eliminates the inspiratory

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Table 42.1 The context of ventilatory support in the neonate

Situation	Examples	Predominant pathophysiological disturbance(s)	Mode	PEEP*	V_T range (mL/kg)	Considerations regarding ventilator mode and settings
<i>Apnoea</i>	Preterm infant with apnoea of prematurity Ex-preterm infant with respiratory syncytial virus	Poor respiratory drive, physiological consequences of episodic apnoea (bradycardia and desaturation)	SIMV	Low-medium	4–5	Should only need low mandatory ventilator rate. Lungs often relatively compliant, but potential for overdistension and volutrauma if pressure settings too high
<i>Surgery/postsurgery</i>						
General aspects	Any infant with a painful surgical incision	Suppression of respiratory drive due to sedation. Limitation of respiratory excursion due to pain	(S)IMV	Medium	5–6	Low tidal volumes (< 5 mL/kg) may predispose to atelectasis May not trigger effectively if heavily sedated
Abdominal surgery	Term infant – gastroschisis repair Preterm infant – laparotomy for necrotising enterocolitis	Raised intra-abdominal pressure and diaphragmatic splinting	SIMV or AC	Medium-high	5–6	High PEEP needed to maintain EELV and recruitment Where intra-abdominal pressure very high, may be poor response to conventional ventilation; HFOV or HFJV preferred
Thoracic surgery	Term infant – lobectomy for congenital lobar emphysema Preterm infant – ligation of persistent ductus arteriosus	Lung compliance alterations intra-operatively; post-operative risk of air leak	SIMV or AC	Medium	4–5	Changes in both PEEP and V_T may be needed intra-operatively
<i>Lung disease</i>						
Diffuse alveolar disease	Preterm infant with RDS Term or preterm infant with haemorrhagic pulmonary oedema	Poor lung compliance, compliant chest wall Poor lung compliance	AC SIMV or AC	High High	4–5 4–6	Recruitment using PEEP increments may be helpful. Short T_I and fast rate well tolerated Recruitment using PEEP increments and fixed tidal volume may be helpful. Longer T_I needed to help recruitment
Localised or heterogeneous disease	Preterm infant with nosocomial pneumonia Term infant with meconium aspiration syndrome	Areas of low compliance with adjacent areas of relatively normal lung	SIMV or SIMV + PSV	Medium	5–6	Potential for overdistension of relatively normal lung regions. Fast ventilator rates may result in a T_E that is too short for normal lung regions. Higher V_T needed in meconium aspiration due to increased alveolar dead space

Inflammatory and/or fibrotic disease	Preterm infant with chronic lung disease	Regions of low compliance and increased resistance, especially expiratory resistance	SIMV + PSV or AC	Medium–high	5–7	Fast ventilator rates may result in a T_E that is too short for the diseased lung regions with long expiratory time constants. Sufficient PEEP is needed to prevent expiratory flow limitation at low lung volumes
Pulmonary hypoplasia	Preterm infant born after early and prolonged rupture of membranes Term infant with congenital diaphragmatic hernia	Low lung compliance related to small total lung volume. Overdistension of lungs at standard ventilator pressures	SIMV or AC	Low–medium	3–5	Hypoplastic lung is vulnerable to overdistension, stretch injury and high pulmonary vascular resistance. Avoid high V_T /PIP. Consider high-frequency ventilation if PIP > 25 cm H ₂ O, or if there is refractory hypoxic respiratory failure
Gas trapping/air leak	Preterm infant with pulmonary interstitial emphysema Pneumothorax (after drainage)	Compression of normal airspaces by interstitial gas Continued leak of gas into the pleural space	SIMV SIMV or AC	Medium Medium	4–5 4–5	Low PEEP approach may lead to persistent hypoxaemia and respiratory acidosis. High-frequency ventilation (especially HFJV) is preferable Consider high-frequency ventilation (if available) where there is a torrential gas leak
Pulmonary insufficiency of prematurity	Extremely preterm infant in room air shortly after birth, failing extubation due to inadequate respiratory effort	Global immaturity of respiratory system, with low respiratory muscle capacity	AC or SIMV + PSV for weaning	Medium	4–5	Lungs become relatively compliant once atelectasis resolved, and there is potential for overdistension and volutrauma if pressure settings too high.
Persistent pulmonary hypertension	PPHN with parenchymal lung disease PPHN with normal lung parenchyma	Reduced pulmonary blood flow secondary to increased pulmonary arteriolar tone, exacerbated by low alveolar pO ₂ and pH Reduced pulmonary blood flow secondary to increased pulmonary arteriolar tone	SIMV or AC SIMV or AC	Medium Low	4–6 4–5	V_T and PEEP requirements depend on associated parenchymal disease Avoid hyperventilation
<i>Cardiac disease</i> Left to right shunts	Preterm infant – patent ductus arteriosus Term infant – large ventricular septal defect	Decreased lung compliance related to pulmonary engorgement and oedema	AC	High	5–6	Increasing CO ₂ can help limit blood flow to some degree

(continued)

Table 42.1 (continued)

Situation	Examples	Predominant pathophysiological disturbance(s)	Mode	PEEP*	V _T range (mL/kg)	Considerations regarding ventilator mode and settings
Vulnerable pulmonary circulation	Pulmonary atresia with duct-dependent pulmonary circulation Hypoplastic left heart syndrome, post-Norwood operation	Pulmonary blood flow highly variable and under the influence of intra-alveolar pressure	SIMV	Low–medium	5–7	Lung overdistension with high-pressure settings will restrict pulmonary blood flow. Manipulation of pCO ₂ can help to control pulmonary blood flow – lower CO ₂ to promote blood flow, increase CO ₂ to restrict blood flow
Neuromuscular disease	Term infant with myotonic dystrophy	Low FRC and V _T secondary to compromised respiratory muscle function	AC or SIMV + PSV	Medium	4–6	Appropriate to give mechanical support for each breath
<i>Airway obstruction</i>						
Supra-glottic airway obstruction	Severe Pierre Robin sequence	Alveolar hypoventilation, normal lung compliance	SIMV	Low–medium	4–6	
Glottic/sub-glottic airway obstruction	Term infant with oesophageal atresia and tracheomalacia	Alveolar hypoventilation, expiratory prolongation and gas trapping	SIMV	Low–medium if obstruction relieved, high otherwise	4–6	Settings influenced by whether the obstruction can be relieved by positioning of the endotracheal tube tip beyond the point of maximal narrowing

PEEP positive end-expiratory pressure, V_T tidal volume, SIMV synchronised intermittent mandatory ventilation, AC assist/control, EELV end-expiratory lung volume, HFOV high-frequency oscillatory ventilation, HFOV high-frequency jet ventilation, T_I inspiratory time, T_E expiratory time, PSV pressure support ventilation
*PEEP levels: low = 4 cm H₂O (preterm), 5 cm H₂O (term); medium = 5–6 cm H₂O (term); high = 7–8 cm H₂O (preterm), 9–12 cm H₂O (term)

hold, making for better synchronisation and automatically adjusting the effective inspiratory time (T_i) as time constants change. However, this mode may not be appropriate in extremely small premature infants in the first few days of life, in whom respiratory time constants are so short that the actual T_i may be less than 0.25 s. This duration of inspiration may be inadequate for gas mixing in the terminal air spaces and additionally may lead to excessively rapid respiratory rates.

Ventilators designed primarily for adult/paediatric patients but capable of also supporting neonates tend to have a greater variety of modes (some untested in newborn infants) and to offer volume-controlled ventilation. Unlike on the specialty neonatal ventilators, PSV on these devices does not have a backup rate and thus requires a reliable respiratory effort, not often present in pre-term infants. However, when ventilating newborn infants, the clinician must be aware of the pitfalls of applying various modes to this unique population. The major limitation of volume-controlled ventilation is that the device only controls the volume delivered into the proximal (ventilator) end of the circuit, not the volume entering the patient's lungs. Because of compression of gas and stretching of the circuit, as well as leak around uncuffed endotracheal tubes (ETT), there is only a very indirect relationship between set and delivered V_T . For this reason, time-cycled, pressure-limited ventilation has been the standard ventilation mode in the NICU. There are several volume-targeted modes of pressure-limited ventilation with different operating principles and capabilities that more accurately control delivered V_T in newborn infants. Some of these modalities have been studied in considerable detail and shown to reduce the incidence of hypocapnia, excessively large V_T , duration of mechanical ventilation and to decrease levels of pro-inflammatory cytokines (Keszler 2009). Volume-targeted ventilation is discussed in detail elsewhere in this book. The more conventional modes are discussed below, and suggestions regarding the most appropriate modes for neonatal ventilation are incorporated in Table 42.1.

Despite many years of daily use, no consensus has emerged regarding the relative merits of the commonly used modes of synchronised ventilation. Guidance from large prospective trials with

important clinical outcomes, such as incidence of air leak, chronic lung disease or length of ventilation, is lacking. Short-term clinical trials have demonstrated less tachypnoea and less variable V_T (Mrozek et al. 2000), more rapid weaning from mechanical ventilation (Chan and Greenough 1994; Dimitriou et al. 1995) and smaller V_T with smaller fluctuations in blood pressure (Hummler et al. 1996) with AC, compared to SIMV. There are important physiological considerations suggesting that SIMV may not provide optimal support in very premature infants. SIMV supports a user-defined number of breaths synchronised with the infant's spontaneous respiratory effort. Spontaneous breaths in excess of the set rate are not supported, resulting in uneven tidal volume and high work of breathing during weaning. This is particularly important in extremely small and immature infants intubated with a narrow bore ETT (Fiastro et al. 1988). The high airway resistance of the ETT, limited muscle strength and mechanical disadvantage of the infant's excessively compliant chest wall result in small, ineffective V_T . Small breaths that largely rebreathe dead space gas will contribute little to effective alveolar ventilation. To maintain adequate alveolar minute ventilation, relatively large V_T is thus required with the limited number of mechanical inflations provided by the ventilator. In a group of ELBW infants in the recovery phase of respiratory distress syndrome (RDS) ventilated with SIMV, the V_T of mechanical inflations was about 6 mL/kg with spontaneous V_T of 2.5 mL/kg, very close to anatomical dead space (Osorio et al. 2005). However, most clinicians continue to use SIMV, particularly during the weaning phase (Sharma and Greenough 2007). This is based on the intuitive assumption that fewer mechanical inflations are less damaging and on the traditional thinking that the ventilator rate must be lowered before extubation. However, because lung injury is primarily caused by excessive V_T , irrespective of the pressure required to generate that V_T (Dreyfuss and Saumon 1993; Hernandez et al. 1989; Dreyfuss and Saumon 1998), the smaller V_T used with AC (Hummler et al. 1996) likely outweighs the faster rate. This concept is supported by the Oxford Region Controlled Trial of Artificial Ventilation

study where a ventilator rate of 60 inflations per min compared to 20–40 was shown to result in less air leak with unsynchronised IMV (OCTAVE Study Group 1991). Many clinicians also mistakenly believe that assisting every breath prevents respiratory muscle training. This concern reflects a poor understanding of the patient–ventilator interaction during synchronised ventilation. With synchronised ventilation, the V_T is generated by the combined inspiratory effort of the patient (the baby pulling air in) and the positive pressure generated by the ventilator pushing air in. The resulting transpulmonary pressure, together with the compliance of the respiratory system, determines the V_T . Thus, as ventilator inflation pressure is decreased during weaning, the infant gradually assumes a greater proportion of the work of breathing and achieves respiratory muscle training. Ultimately, the ventilator pressure is decreased to the point when it only overcomes the added resistance of the ETT and circuit, at which point the infant should be extubated.

There is little difference between the modes during the acute phase of the disease when SIMV rate is relatively high. The differences become more meaningful during weaning, especially at rates <20. The less intuitive weaning process with AC appears to be one of the reasons clinicians continue to employ SIMV during weaning from mechanical ventilation. Another reason is the anecdotal observation that sometimes infants become tachypnoeic with AC and may have mild hypocapnia. This tachypnoea may reflect the infant's response to low mean airway pressure (P_{AW}) during weaning – shortening the expiratory time (T_E) serves to maintain lung volume at end expiration. Tachypnoea appears to be infrequent when decreasing peak inspiratory pressure (PIP) is balanced by higher PEEP to avoid loss of lung volume. Low rate SIMV, especially in small infants with 2.5-mm-diameter ETT, is likely to impair the weaning process. Some ventilators offer the option of supporting spontaneous breaths with pressure support ventilation. This will compensate for the problems associated with simple SIMV but becomes a more complex process requiring the clinician to select settings for both SIMV and the level of pressure support.

Nonetheless, more rapid weaning when SIMV was combined with PSV compared to SIMV alone has been demonstrated (Reyes et al. 2006). Based on these findings, it is recommended that when SIMV is used during the weaning process, PSV should be utilised to support spontaneous breathing. The alternate and less complicated approach is to use AC or PSV as a stand-alone mode to assist all spontaneous efforts and simply wean the inflations pressure, taking care to maintain adequate P_{AW} . This is most easily accomplished when using volume-targeted modes of ventilation discussed earlier in this book. Finally, the attributes of the particular ventilator may influence the choice of triggered modes. Many flow-triggered devices are susceptible to auto-triggering due to leak around the ETT. This is more problematic with AC than with SIMV, where the mechanical breath rate is limited. Devices that have a very effective leak-adapted trigger and breath termination algorithms, such as the Draeger Babylog, are virtually immune from this problem and thus facilitate the use of AC.

42.3 First Settings

This section focuses on the initial management of the ventilated infant following intubation. Overall rationale for, and evidence supporting, choice of ventilator settings in newborns is set out in Sect. 42.4.

After intubation, a period of ventilation using a portable ventilation device will usually be required until the endotracheal tube is secured, nasogastric tube inserted, and the baby positioned in readiness for ventilation. In preterm infants, bolus surfactant may also be given at this time. If the ventilation device does not allow delivery of PEEP, the infant should be connected to the ventilator as quickly as possible.

The initial ventilator settings should take into account the context in which ventilation is being applied to the neonate (Table 42.1) and the apparent response to the pressure settings being used during ventilation with a portable device. There should be a stepwise approach to setting the ventilator at the time of initiation of mechanical

Table 42.2 Stepwise approach to initial ventilator settings

These parameters to be set in the order suggested
PEEP – set according to context (see Table 42.1) and oxygen requirement
T_I – sufficient to allow complete gas inflow to occur (and longer, if tidal recruitment needed)
PIP – sufficient to produce adequate chest movement (and V_T , when measured)
T_E (or ventilator rate) ^a – set so as to allow complete gas outflow to occur and, in combination with V_T , to produce adequate minute ventilation

PEEP positive end-expiratory pressure, T_I inspiratory time, PIP peak inflation pressure, V_T tidal volume, T_E expiratory time

^aIn some ventilators, the rate is set directly, and in others it is determined by the combination of inspiratory and expiratory time

Table 42.3 Clinical evaluation after initiation of mechanical ventilation

<i>Observation</i>
Colour and circulation
Infant's spontaneous respiratory rate
Patient–ventilator interaction – evidence of triggering/autocycling
Chest rise and diaphragmatic excursion
Work of breathing
Gastric distension
<i>Auscultation</i>
Breath sounds to all lung areas
Adventitious sounds
Large airway sounds
Heart sounds
<i>Ventilation parameters</i>
Delivered tidal volume
Flow–time curve – evidence of sufficient inspiratory and expiratory time

ventilation (Table 42.2), guided in part by a thorough clinical appraisal (Table 42.3). PEEP should be considered first, with suggested PEEP levels for a range of different situations set out in Table 42.1. The T_I should be set at around 0.5 s for a term infant and 0.35 s for a preterm infant, and then further adjusted depending on the analysis of the flow–time curve, which can be displayed on most modern neonatal ventilators. For most applications of time-cycled pressure-limited ventilation, T_I should be set long enough to allow complete or near-complete inflow of gas

into the lung during inspiration. If the T_I is too short, there may not be sufficient time for an adequate tidal volume to be delivered nor for alveolar recruitment to occur with each tidal inflation. Setting PIP should be guided by a visual appreciation of chest rise and preferably the measured V_T . Suggested target values for V_T are set out in Table 42.1. Finally, T_E (and thus, respiratory rate) is adjusted, with the aim of producing sufficient minute ventilation to clear CO_2 without causing dynamic hyperinflation related to inadvertent PEEP. An estimate of minute ventilation can be made using the product of measured V_T and respiratory rate, with a value of 200–300 mL/kg/min usually being an adequate starting point before the first pCO_2 reading is obtained. Note that this estimate of minute ventilation does not incorporate dead space volume, which is substantial in some infants, particularly those with hyperinflated lungs (“alveolar dead space”). Additionally, rapid shallow breathing leads to high dead space to V_T ratio and reduced alveolar ventilation. Avoidance of inadvertent PEEP can be difficult when an infant has a rapid spontaneous breathing rate and each breath is being supported by the ventilator. Examination of the flow–time curve during expiration will reveal whether gas outflow is complete before the next inflation begins and thus whether dynamic hyperinflation is likely to occur. If so, further adjustment to the mode of ventilation, respiratory rate and even inspiratory time may be necessary, as discussed below.

42.3.1 Assessment After Going onto the Ventilator

A thorough clinical re-evaluation after initiation of ventilation is essential (Table 42.3), with the expectation that further adjustments to ventilator settings may be necessary. Careful note of the rate of spontaneous ventilation, and the effectiveness of triggering, should be made as the infant recovers from the intubation and the effects of any sedative and muscle relaxant drugs used prior to it. The need for further sedation/analgesia should be assessed. Muscle relaxation is rarely indicated in

the era of effective synchronised ventilation. Narcotic analgesia should be used judiciously; clinical trial evidence suggests morphine administration relieves pain in ventilated neonates but may increase the risk of adverse neurological outcomes (Anand et al. 2004). If spontaneous breathing is to continue, the trigger sensitivity may need to be altered to optimise patient–ventilator interaction. In general, the trigger threshold should be as low as possible without causing autocycling, because higher trigger threshold is associated with higher work of breathing and longer trigger delay. An attempt should always be made to confirm whether “triggered” inflations are actually preceded by spontaneous respiratory effort or, alternatively, whether the ventilator is autocycling. The latter situation is more likely when there is a significant tube leak (despite “tube compensation”) (Bernstein et al. 1995), or with condensed water collecting in the ventilator tubing, and can lead to very significant hyperventilation particularly in AC mode.

Observation of the chest rise and abdominal motion will give some guide to the delivered V_T , although this is a clinical skill that requires some time to learn (Aufrecht et al. 1993), and may underestimate the actual V_T (Schmolzer et al. 2010). High residual work of breathing may reflect inadequate tidal volume or inadequate minute ventilation, and ventilator settings should be adjusted appropriately. In the immediate post-intubation period, respiratory system compliance may be transiently decreased due to gaseous abdominal distension, especially after prolonged face mask ventilation. Venting of the stomach with a tube should occur soon after intubation to overcome any impairment of respiratory system compliance related to gastric distension with gas (Heldt 1988). Airway obstruction or ETT malposition should also be ruled out if the infant appears to be struggling.

Auscultation of the chest gives vital information in the intubated patient (Table 42.3) and should be conducted thoroughly and carefully after mechanical ventilation has been initiated. The intensity and distribution of breath sounds within the thorax gives information about the nature of the respiratory pathology and the effectiveness of ventilation.

Uneven breath sounds (lower intensity over left hemithorax) suggest the possibility of tube malposition with the tip in the right main bronchus. The presence of a large airway noise which abates when the tube is pulled out a small distance adds further support. Large airway noise (low-pitched inspiratory noise) can relate to a build-up of secretions in the intrathoracic conducting airways and may also be transmitted from the glottic level in the presence of an endotracheal tube leak. If caused by tube leak, the noise will be of similar intensity (or louder) on auscultation with the stethoscope applied over the forehead (due to its extrathoracic origin). Applying cricoid pressure to ablate the leak provides additional confirmation.

The final component of the initial clinical assessment after commencing ventilation is an analysis of available ventilator data. Observation should be made over a number of inflations of the delivered V_T for a set PIP or, conversely, the PIP required to deliver a set V_T . If in a volume-targeted mode, the PIP limit may need to be increased if the desired V_T is not being delivered. Analysis of the flow waveform will allow refinements of T_I and expiratory time (T_E).

After intubation and commencement of mechanical ventilation, a chest X-ray should always be performed to confirm the position of the endotracheal tube, to assess the state of the lung parenchyma and to gain an appreciation of the degree of lung inflation. Given that chest X-rays are taken at peak inflation, the degree of lung inflation will be a reflection of end-inspiratory lung volume (EELV plus V_T), and thus does not help significantly in titrating PEEP. For this reason, some investigators have chosen to perform chest X-rays at end expiration (Pohlandt et al. 1992), but this is not currently a widespread practice.

42.3.2 Monitoring and Documentation During Mechanical Ventilation

With the need for mechanical ventilation comes the need for intensive monitoring and careful charting of physiological and ventilatory

Table 42.4 Monitoring of the ventilated infant

<i>Physiological monitoring</i>	
Essential	Cardiorespiratory monitoring (numeric display of heart rate and respiratory rate, with preferably a real-time display of 3-lead ECG wave and respiratory impedance tracing) Transcutaneous SpO ₂ (numeric display with preferably a plethysmographic SpO ₂ tracing) Temperature
Desirable	Intra-arterial catheter placement for continuous blood pressure monitoring and intermittent arterial blood gas sampling Transcutaneous pCO ₂ (+/- pO ₂) End-tidal CO ₂ (infants beyond term)
<i>Ventilation parameters to be monitored and recorded</i>	
Essential	Delivered ventilator pressures (PEEP, PIP and P _{AW}) T _I Respiratory rate (mechanically assisted and total) V _T (breath by breath, preferably the expired V _T measured at the airway opening) %leak (difference between inspired and expired V _T , expressed as a percentage of the inspired V _T) Humidifier temperature
Desirable	Ventilator waveforms (time scalars of pressure and flow) Compliance and resistance measurements Tidal pressure–volume curves

PEEP positive end-expiratory pressure, *PIP* peak inspiratory pressure, *P_{AW}* mean airway pressure, *T_I* inspiratory time, *V_T* tidal volume

parameters. All mechanically ventilated infants should have, at the very least, cardiorespiratory monitoring, continuous measurement of oxygen saturation (SpO₂) via a transcutaneous pulse oximetry probe and temperature monitoring (Table 42.4). An intra-arterial catheter to continuously monitor blood pressure and allow periodic arterial blood gas sampling is essential in the unstable and critically ill infant and highly desirable in any infant requiring mechanical ventilation. A continuous estimate of pCO₂ derived from transcutaneous monitoring or end-tidal gas sampling is also valuable, whether or not an arterial line is in place. Because ET CO₂ monitoring adds significantly to the instrumental dead space and is often inaccurate in small infants whose rapid respiratory rates do not allow an end-tidal plateau to be reached, transcutaneous monitoring is to be preferred in most ventilated neonates.

Ventilation parameters that should be monitored and recorded include ventilator pressures and timing and the total breath number and number of mechanically assisted breaths per minute (Table 42.4). The delivered V_T (and the target V_T, if set) should be noted, along with the proportion of leak. To be accurate, V_T must be measured at the airway opening, not at the ventilator end of the circuit. Whilst some devices offer a compliance compensation feature that corrects for the loss of V_T in the circuit, this feature does not function well in the presence of ETT leak. The humidifier temperature should be regularly checked and recorded. Most modern ventilators also provide continuous display of waveforms and/or tidal ventilation loops, and these, along with breath-by-breath compliance and resistance measurements, can be very helpful in fine-tuning ventilator settings, as described in this and other chapters in this text.

42.4 Ventilator Settings and Strategies: Pathophysiological Rationale, Meta-analytic Evidence and Therapeutic End Points

42.4.1 Manipulating End-Expiratory Lung Volume

Physiological first principles, and a large body of experimental and clinical evidence, point to the importance of manipulating EELV during mechanical ventilation of the diseased lung. It has become clear that to apply ventilation optimally requires a well-recruited lung with adequate end-expiratory volume (Rimensberger 2002; Clark et al. 2000). Such an approach is dependent on the application of sufficient PEEP, and the physiological considerations that guide PEEP setting are discussed in this section.

Clinical and experimental data point to a clear relationship between PEEP and EELV and, thus, oxygenation. Changes in other ventilator settings may, however, potentially lead to alterations in

EELV. A long-held belief was that an increase in P_{AW} by alteration of any combination of ventilator settings would have a similar impact on oxygenation and thus that there should be an optimal P_{AW} at which to apply ventilation (Boros et al. 1977). It is now becoming accepted that the components that make up the P_{AW} (PIP, PEEP, T_i , rate and gas flow) should be considered separately. As stated by Monkman and Kirpalani:

In retrospect, the simplifying but reductionist elegance that focused upon a single unitary number [P_{AW}] may have misled the field. (Monkman and Kirpalani 2003)

Thus, an improvement in oxygenation after a PEEP increase should not be viewed as having occurred simply because the P_{AW} is higher but rather because EELV has increased and $\dot{V}/Q$ matching has improved. Despite also producing P_{AW} changes, alteration in other ventilator parameters does not have the same effect on EELV (Fig. 42.1) (Thome et al. 1998) nor on oxygenation (Stewart et al. 1981). The inextricable linkage between PEEP, EELV and oxygenation dictates that it is PEEP that is the first, and arguably the

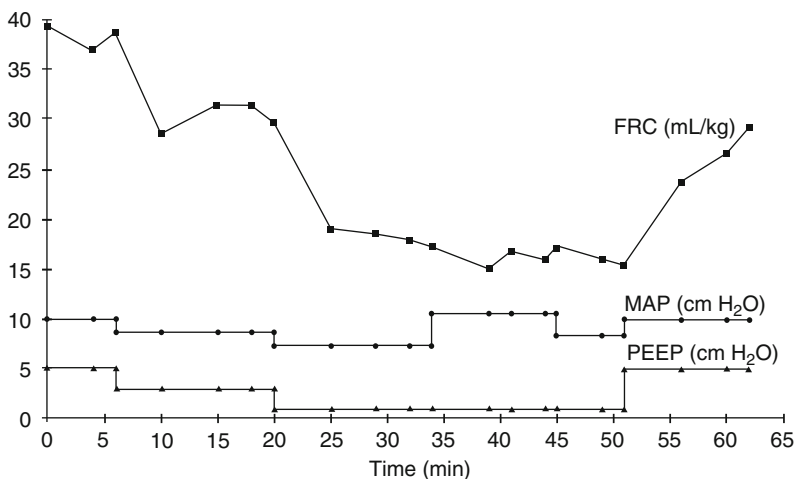


Fig. 42.1 Effect of ventilation changes on end-expiratory lung volume. Changes in end-expiratory lung volume (EELV, denoted as functional residual capacity, FRC) during programmed manipulation of ventilator settings in a ventilated infant. EELV is seen to reduce with stepwise reductions in positive end-expiratory pressure (PEEP) and thus

mean airway pressure (P_{AW} , denoted as MAP) during the first 30 min. At minute 34, inspiratory time is lengthened from 0.3 to 0.6 s, leading to an increase in P_{AW} , but no significant change in EELV. Conversely, when PEEP is increased (minute 52), there is a substantial improvement in EELV (Reproduced from Thome et al. (1998) with permission)

most important, ventilatory parameter to be considered in the continuing management of the ventilated neonate.

An important difficulty in manipulating EELV in the ventilated subject is that the available methods to measure EELV at the bedside are imprecise and in some cases impractical (Dargaville and Rimensberger 2010). Whole-body plethysmography (Stocks et al. 2001) and gas dilution (Sivan et al. 1990; Vilstrup et al. 1992), both of which give absolute values for EELV, are not appropriate for repeated measurements in a clinical setting. Other methods, including respiratory inductance plethysmography (Adams 1996; Emeriaud et al. 2010), fibre-optic plethysmography (Davis et al. 1999) and electrical impedance tomography (Frerichs et al. 2001), allow measurement not of absolute volume but of change in EELV relative to a baseline condition, and only with prior calibration can a gas volume change in mL be derived. Despite these limitations, a great deal of information has been obtained from experimental studies in which EELV has been measured, either at the bedside or in the laboratory, as alterations in PEEP have been made. The key findings of this work are set out below. This knowledge can be used by clinicians to set and titrate PEEP in ventilated subjects, aided by indirect measures of EELV, in particular oxygenation and tidal breath compliance.

42.4.1.1 Relationships Between PEEP, EELV and Recruitment

An understanding of what can potentially be achieved through manipulation of lung volume using PEEP comes from firstly examining the changes in EELV and recruitment during stepwise PEEP manoeuvres. Such information is derived from lung modelling, studies in experimental animals and in humans with lung disease. An example is shown in Fig. 42.2. With stepwise PEEP increments and a constant inflating pressure (PIP-PEEP), a surfactant-depleted lung starting at residual volume follows the path of the inflation limb of the pressure-volume (PV) relationship (Fig. 42.2), with an improvement in tidal breath compliance as more non-aerated lung units are recruited, followed by a fall in

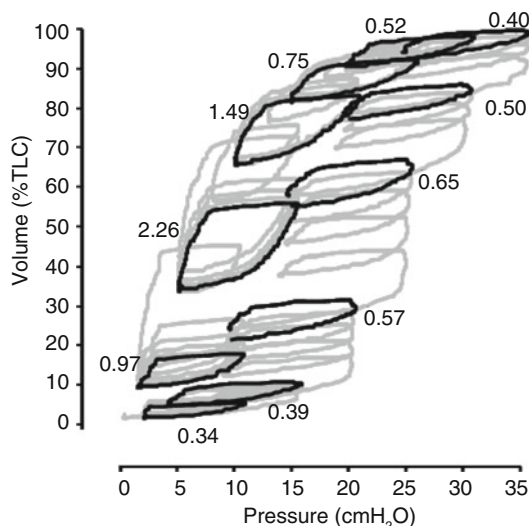


Fig. 42.2 Stepwise vital capacity manoeuvre in the injured lung. Pressure-volume curve during a stepwise vital capacity manoeuvre using positive end-expiratory pressure (PEEP) increments and decrements in a mechanically ventilated 2.1 kg piglet after repeated saline lavage. Each PEEP level was held for 15 s. Inflating pressure (peak inspiratory pressure – PEEP) remained at 10 cm H₂O throughout. Y-axis shows lung volume measured by respiratory inductance plethysmography and scaled to total lung capacity (TLC). Complete tracing is shown in grey and the final breath at each PEEP level in black, and the tidal breath compliance (mL/cm H₂O/kg) for each of the final breaths is indicated in *italics* (Data derived from same experimental series as reference (Dargaville et al. 2010))

compliance as more lung units become overdistended near total lung capacity. During PEEP decrements (Fig. 42.2), the property of hysteresis is demonstrated with a different PV trajectory than during PEEP increments, following a path closer to the deflation limb of the PV relationship. There is preservation of recruitment through a large proportion of this trajectory, and the open tidal ventilation loops reflect the marked improvement in compliance during PEEP decrements, as has been predicted by lung modelling (Hickling 2001). At the point of maximal curvature of the deflation limb (“closing pressure”), the lung is still well inflated, recruitment is largely preserved and tidal ventilation at this point is associated with minimal overdistension and a peak in compliance. This is the point of “optimal PEEP”, at which the lung is ventilated with the best possible oxygenation and compliance and with the least

Table 42.5 The benefits of positive end-expiratory pressure (PEEP) optimisation in the diseased lung

Maintenance of lung recruitment
Defence against absorption atelectasis in high FiO_2
Improved lung compliance and thus a reduction in peak inflation pressure to achieve the same tidal volume
Better oxygenation and a reduction in FiO_2
More efficient CO_2 removal
More even distribution of ventilation
Preservation of surfactant
Reduction in lung injury

possible pressure (Rimensberger et al. 1999a). Additional advantages of optimising PEEP in this way are shown in Table 42.5. In the experimental animal with recruitable lungs, PEEP set in relation to the point of maximal curvature of the deflation limb is often at or below the PEEP value predicted from the lower inflection point of the inflation limb (Rimensberger et al. 1999a).

Finding optimal PEEP as described above is not difficult in experimental animals, as long as the lung is recruitable and can withstand brief inflation to total lung capacity. The technique has also been applied to adult subjects with acute respiratory distress syndrome (Amato et al. 1998; Suarez-Sipmann and Bohm 2009), allowing confirmation of many of the physiological features noted in the laboratory. A limiting factor is that if the lung has few recruitable units, there will be minimal hysteresis and the PEEP at the point of maximal curvature of the deflation limb may actually be higher than the PEEP at the lower inflection point on the inflation limb, with minimal benefit in compliance, and the risk of overdistension with each tidal breath (Albaiceta et al. 2005).

In mechanically ventilated newborn infants, there have been few attempts to find optimal PEEP using stepwise increments and decrements as described above. The PV relationship of the lung has, however, been mapped in ventilated infants on high-frequency oscillatory ventilation (HFOV), allowing definition of hysteresis and a point of maximal curvature (closing pressure) on the deflation limb (Tingay et al. 2006). Similar PV tracing during HFOV, using oxygenation as an indicator of lung volume, is routinely used in some institutions to identify optimal P_{AW} (De Jaegere et al. 2006). The deflation limb of the PV relationship

has also been traced in preterm infants using a quasistatic technique performed over a maximum of 10 s (Vilstrup et al. 1996). A point of maximal curvature appears to be identifiable in each recording, but in this early study, no attempt was made to use this landmark for PEEP setting. In parallel with adult studies, there has been some attempt to set PEEP in newborn infants based on the shape of the inspiratory PV curve, traced over 30 s after a 5 s disconnection to ambient pressure (Mathe et al. 1987). An inflection point was identifiable in each infant, with greater concavity in those with more severe disease (indicating potential for recruitment). Change in the position of the inflection point, and the concavity of the inflation limb, was noted with resolution of disease (Fig. 42.3). Setting PEEP by this method improved oxygenation in infants at the height of disease, but not those in the recovery phase (Mathe et al. 1987).

With the exception of these more penetrating studies, the investigation of PEEP and PEEP setting in ventilated neonates has been limited to studies of short-lived PEEP adjustments, in some cases with stepwise PEEP increments analogous to the titration of CPAP described in the very earliest reports of this therapy (Gregory et al. 1971). Increases in PEEP universally lead to an increase in EELV (Thome et al. 1998; Dinger et al. 2001; Bose et al. 1986) and an improvement in oxygenation (Stewart et al. 1981; Dinger et al. 2001; Bose et al. 1986). In the diseased lung, the oxygenation response to increasing EELV is related to both decreased venoarterial shunting due to recruitment of non-aerated lung units and improvement of $\dot{V}/Q$ matching with better gas aeration. The potential for PEEP to induce change in EELV in the ventilated neonate is significantly greater than for isolated changes in PIP or T_I (Thome et al. 1998). PEEP increases were most usually associated with a fall in tidal compliance suggesting overdistension (Dinger et al. 2001; Alegria et al. 2006). Infants with more severe lung disease may, however, demonstrate an improvement in compliance with PEEP increments indicating lung recruitment (Dinger et al. 2001). The level of applied PEEP also has the potential to impact upon cardiac function, but it is clear that the adverse effects of PEEP on cardiac output are much more prominent in the normal lung (Holzman and

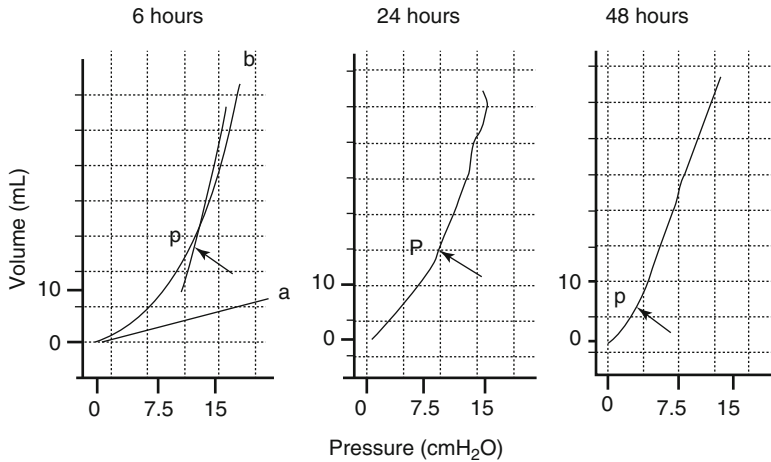


Fig. 42.3 Inflation limb of the pressure–volume relationship in an infant with respiratory distress syndrome. Sequential inflation limb pressure–volume curves from a newborn with respiratory distress syndrome recorded at 6, 24, and 48 h. X-axis, applied pressure; Y-axis, volume of insufflated oxygen. The initial slope (*a*) and slope in the

linear portion of the pressure–volume curve (*b*) are shown at 6 h. Black arrows and point *P* indicate the lower inflection point, at which positive end-expiratory pressure was then set. Note the shift in position of this point with improvement in lung function (Redrawn from Mathe et al. (1987), with permission)

Scarpelli 1979). This relates to the transmission of intra-alveolar pressure to the pleural and mediastinal compartment, which is substantially greater in a recruited lung. Indeed, one study in the pre-surfactant era used rise in pleural pressure (as indicated by oesophageal pressure) to indicate the point at which lung recruitment had occurred during PEEP increments (Bonta et al. 1977).

The findings of these studies are heavily influenced by the severity of lung disease in the subjects under study and the starting point and span of PEEP settings used. There has also been considerable reluctance to keep the driving pressure constant with PEEP adjustments, in part related to a misconception that PEEP by itself produces lung recruitment. Recruitment is an inspiratory phenomenon; the value of PEEP is in maintaining recruitment of open lung units at end expiration (Gattinoni et al. 2003). None of the PEEP-titration studies in neonates have until recently emulated the “open lung” concept of lung recruitment followed by titration of PEEP using small pressure decrements (Suarez-Sipmann and Bohm 2009; Lachmann 1992). The only study designed to maintain stable pressure amplitude during PEEP increments investigated the effect of a lung recruitment maneuver (LRM) with incremental PEEP adjustments in infants with mean

GA of 25 wk ventilated for RDS with AC+VG in a small randomized trial (Lista et al. 2011). LRM consisted of 0.2 cm H₂O increments in PEEP every 5 minutes, until FiO₂ reached 0.25, followed by reduction of PEEP until oxygenation began to deteriorate. If FiO₂ rose, PEEP was increased again to re-recruit the lung and then reduced again to situate the lungs on the deflation limb of the pressure/volume curve. Initial FiO₂ was 56±24 versus 52±21, in the two groups. The full LRM lasted for 61±18 minutes. The infants appeared to have only mild lung disease, with maximum PEEP reaching only 6.1±0.3 cm H₂O. LRM lead to faster weaning of FiO₂ (94±24 versus 435±221 minutes; *p*=0.000) and shorter O₂ dependency (29±12 versus 45±17 days; *p*=0.04). No adverse events and no differences in the outcomes were observed. Though limited by the modest severity of illness and small sample size, the study suggests that LRM with incremental PEEP adjustments is feasible during conventional ventilation.

42.4.1.2 Guiding Principles for PEEP Setting in the Neonate

1. There is no universal PEEP setting that is correct for all lung diseases, or even for one disease, or even for one individual through the

course of their disease. Units that choose to mandate a PEEP level for reasons of simplicity or the need to protocolise ventilator settings are missing opportunities to manage respiratory failure optimally and according to sound physiological reasoning. Suggested ranges for PEEP are given in Table 42.1; these should be considered in the light of the individual circumstances, with further adjustment according to the physiological response and the course of the disease. The PEEP setting should be re-evaluated whenever there is an alteration to pulmonary mechanics, for example, after surfactant administration (Goldsmith et al. 1991).

2. Unquestionably, very low PEEP (and zero PEEP) is inappropriate in the diseased lung (Monkman and Kirpalani 2003), predisposing to low EELV, poor oxygenation, impaired pulmonary mechanics, greater turnover of surfactant and a risk of greater lung injury.
3. Conversely, a PEEP level that is set too high for too long leads to overdistension of the lung, impairment of venous return and cardiac output and predisposition to pneumothorax.
4. PEEP is not, of itself, a recruitment tool, and PEEP increments will not recruit the lung optimally without an adequate inflating pressure (PIP-PEEP) to reinflate non-aerated lung units. Once the lung is recruited, the PEEP (and PIP) must then be turned down.
5. PEEP is effective in maintaining lung volume in circumstances predisposing to atelectasis, for example, during anaesthesia (Easa et al. 1995) and/or after administration of muscle relaxants (von Ungern-Sternberg et al. 2006). PEEP also helps to minimise absorption atelectasis associated with ventilation using 100 % oxygen (von Ungern-Sternberg et al. 2007).

42.4.2 Inspiratory Time

As described elsewhere in this text, the respiratory time constants that determine how rapidly lung volume re-equilibrates after a pressure change are determined by the compliance and resistance of the respiratory system (Bancalari 1986). Infants with poorly compliant lungs secondary to RDS have very short time constants

and thus require only a very short T_I for equilibration to occur (as low as 0.15 s). This may, however, be insufficient time for tidal recruitment to occur during the inspiratory phase. Setting T_I in the diseased lung must therefore find a balance between the wish to minimise the duration of plateau pressure at peak inflation and the need to provide adequate time for the recruiting effect of the pressure plateau.

Early ventilation strategies in ventilated neonates evolved to the use of a long T_I , in part because of the lack of PEEP, and the observation that longer T_I and slower ventilator rates improved oxygenation in infants with RDS (Reynolds 1971). With further, and more probing, clinical observations, it became clear that this pattern of ventilation was contrary to the spontaneous respiratory efforts of a preterm infant (South and Morley 1986), unless muscle-relaxed. Clinical trials comparing long T_I (0.66–1.0 s) with short T_I (0.33–0.5 s) subsequently demonstrated an advantage in the shorter T_I group, including a slight reduction in mortality and a clear decrease in the risk of air leak, particularly in infants with RDS (OCTAVE Study Group 1991; Kamlin and Davis 2004).

With the advent of synchronised ventilation has come a further imperative to match the ventilator T_I to that of the infant. Inappropriately long set T_I may lead to dyssynchrony, with the infant exhaling against the ventilator inflation pressure. Conversely if T_I is too short (or lung volume loss too rapid), the infant may interrupt expiration with a further inspiratory effort during the ventilator expiratory cycle (McCallion et al. 2005). From the suggested first T_I settings (0.5 s in the term infant, 0.35 s in the preterm infant, see above), adjustments should be made based on the appearance of the flow waveform. T_I should be prolonged if there is clearly insufficient time for flow to enter the lung. Shortening of the T_I should be considered if there is a prolonged period of zero flow with an inflation pressure plateau; a suggested maximum for this period is one-third of the total inflation time. Recommended ranges for within which to set T_I in the ventilated newborn are 0.25–0.4 s in preterm infants and 0.4–0.6 s in those at full term.

An alternative to making manual adjustments to T_I is to use a flow-cycled mode with expiratory triggering (PSV) (Scopesi et al. 2007). This mode is not

recommended in the diseased lung prone to atelectasis (Keszler 2009) but may be a sensible alternative during the weaning phase. If there is the option to adjust the percentage of peak inspired flow at which inflation terminates (termination sensitivity), a value no higher than 10 % is recommended.

42.4.3 Choosing the Appropriate Tidal Volume

Since its inception, for a variety of reasons neonatal ventilation has largely been conducted using pressure-limited ventilatory modes. This remains so up until the present day (van Kaam et al. 2010). Until recently, it has been difficult to measure tidal volumes, but the latest generation of neonatal ventilators allows accurate measurement of V_T , including expired V_T measured at the airway opening. Monitoring and recording of V_T is now routine in most neonatal intensive care units (van Kaam et al. 2010), and with the availability of volume-targeted modes or volume-controlled ventilation, there has been a shift of focus away from the PIP applied and towards the V_T that results. Suggested V_T settings for neonatal ventilation are shown in Table 42.1, and the physiological rationale and clinical evidence in relation to setting or targeting V_T are set out below.

42.4.3.1 Physiological Rationale for Targeting Tidal Volume

Even in the normal lung, tidal ventilation is important not only for gas exchange but also for maintaining lung recruitment, with very low and/or monotonous V_T contributing to atelectasis (Suki et al. 1998; Mutch et al. 2000). For the lung compromised by immaturity, disease or both, maintenance of an adequate V_T during conventional ventilation is of paramount importance. There is compelling evidence for the need to monitor, target and limit tidal volumes in the ventilated neonate, with the clear message that both high and low V_T settings can be dangerous (Keszler 2009).

By virtue of the resultant stretch injury, ventilation with excessive V_T in the neonate has the potential to cause long-standing damage. The combination of immature lung architecture and a highly compliant chest wall renders the newborn

lung, and especially the preterm lung, uniquely vulnerable to overdistension and stretch injury (Clark et al. 2000). Laboratory investigations have highlighted the danger of ventilation with high tidal volumes (Dreyfuss and Saumon 1998; Dreyfuss et al. 1988) with even a few large tidal inflations causing extensive lung injury in the immature lung (Bjorklund et al. 1997). It is also clear that the severity and distribution of injury in this setting depend not only on the magnitude of V_T but also on the state of the lung at end expiration, including the degree of recruitment and residual aeration of lung units (Clark et al. 2000; Chiumello et al. 2008). Application of high V_T to an atelectatic lung causes significant alveolar injury maximal in the nondependent regions, i.e. those areas that remain expanded at end expiration (Tsuchida et al. 2006). Prior reversal of atelectasis by surfactant treatment substantially attenuates the lung injury related to high V_T in the preterm lung (Wada et al. 1997), presumably because the gas delivered with each inflation is more evenly distributed, with less resultant regional overdistension (Dargaville et al. 2010).

Clinical studies in ventilated newborn infants support a role for high V_T in the pathogenesis of lung injury, although the evidence is largely circumstantial. Early clinical trials of rapid versus slow respiratory rates by necessity involved ventilation with different levels of V_T to achieve similar minute ventilation, although the actual V_T was not measured. In comparison to ventilation of infants with RDS with rates of at least 60/min, ventilation at slow rates of 30–40/min (and therefore higher V_T) was associated with a marked increase in pulmonary interstitial emphysema (Pohlandt et al. 1992) and pneumothorax (OCTAVE Study Group 1991). Other markers of over-ventilation in early life, such as hypocapnia, are known to increase the risk for the development of chronic lung disease (Garland et al. 1995; Kraybill et al. 1989), with one putative mechanism being volutrauma related to high V_T (Rimensberger 2002).

Whilst acknowledging the pivotal role of volutrauma in the development of ventilator-induced injury, it must be recognised that ventilation at inappropriately low V_T also has consequences, both in the short and long term. Ventilation of the atelectatic lung at relatively low V_T is associated

with insufficient alveolar recruitment and EELV, poor gas exchange (Probyn et al. 2004) and considerable lung injury (Muscedere et al. 1994), with a predilection for the small airways. If, and only if, the lung is adequately recruited can the benefits of “gentle ventilation” with relatively small tidal volumes be realised. The combination of an “open lung” (Lachmann 1992) and low V_T provides adequate gas exchange and markedly reduces the risk of lung injury during mechanical ventilation (Rimensberger 2002; Rimensberger et al. 1999a, b; van Kaam et al. 2004). Studies of this approach in ventilated adults with acute respiratory distress syndrome have shown reduced mortality and more rapid weaning from ventilation (Amato et al. 1998; ARDS Network 2000). Controlled clinical trials of an open lung approach have yet to be conducted in ventilated newborns (van Kaam and Rimensberger 2007).

42.4.3.2 What Is the Safe Upper Limit of V_T in the Ventilated Neonate?

In parallel with studies in adults showing the benefit of a V_T of 6 mL/kg over a V_T of 12 mL/kg (ARDS Network 2000), limiting tidal volume to <10 mL/kg in ventilated newborns seems appropriate, and most neonates are now ventilated with a V_T of between 4 and 7 mL/kg (van Kaam et al. 2010). Given the vulnerability of the preterm lung in the early days of life, an upper acceptable limit of 6–7 mL/kg is suggested in infants less than 32 weeks. There are particular circumstances in which a V_T as low as 5 mL/kg may still induce injury. Infants with diaphragmatic hernia have immature and underdeveloped lungs which are exquisitely sensitive to volutrauma and by virtue of the reduced total lung capacity tend to respire with V_T values less than 5 mL/kg (Te Pas et al. 2009). For these infants the safe upper limit for V_T may be below 5 mL/kg. Similar considerations apply for neonates with pulmonary hypoplasia from other causes, including preterm infants born after early and prolonged rupture of membranes.

42.4.3.3 What Is the Safe Lower Limit of V_T in the Ventilated Neonate?

Many preterm infants on synchronised ventilation using AC mode supporting every detected patient

effort can achieve adequate gas exchange with V_T values as low as 3–3.5 mL/kg (Scopesi et al. 2007). The concern is that such low values of V_T may over time be insufficient to maintain alveolar recruitment, in particular when low PEEP settings are used (Keszler 2006). A clinical trial comparing V_T targets of 3 and 5 mL/kg found the lower value to be associated with an increase in pro-inflammatory cytokines in bronchoalveolar lavage fluid (Castoldi et al. 2011). V_T targets below 5 mL/kg may be inappropriate in chronically ventilated preterm infants, in whom the V_T required to maintain normocapnia was noted to increase to 6 mL/kg by the third week of ventilation (Keszler et al. 2009). Additionally, there is a small but significant effect of the fixed instrumental dead space of the flow sensor necessary to measure V_T . This additional dead space becomes proportionally larger in the smallest infants, resulting in the need for tidal volume of about 6 mL/kg to maintain normocapnia in infants around 500g, compared to larger preterm infants (Nassabeh-Montazami 2009).

42.4.4 Respiratory Rate

Selection of respiratory rate is a function of the mode of ventilation (SIMV vs AC, $\pm$ volume targeting) as well as the clinical scenario and degree of compromise of CO_2 clearance. Some of the pioneering work on neonatal ventilation arrived at low ventilator rates and long T_I as an appropriate strategy for neonatal ventilation. The technical limitations of the ventilators used, including the inability to directly provide PEEP, influenced this choice. Several clinical trials have found rapid respiratory rates ($\geq 60/\text{min}$), along with shorter T_I , to be less injurious to the lung than slower rates (OCTAVE Study Group 1991; Pohlandt et al. 1992). Additionally the use of a rapid ventilator rate allows more opportunity for synchrony given the rapid respiratory rate and short T_I of most infants with lung disease (South and Morley 1992). Suggestions for setting of respiratory rate are shown in Table 42.6.

The combination of a rapid ventilator rate and a relatively long T_I may lead to dynamic hyperinflation related to the development of inadvertent PEEP (Simbruner 1986). Whilst some investigators have looked upon this as a way to improve lung recruitment, physiological first principles and experimen-

Table 42.6 Setting respiratory rate

Mode	Gestation	Context	Suggested set ventilator rate (inflations per minute)	Comments
SIMV (or IMV if muscle-relaxed)	Term	Height of disease Weaning	40 (30–50) ^a Reduce in decrements of 5–10	Consider adding pressure support if there is high work of breathing with unassisted breaths
	Preterm	Height of disease Weaning	60 (40–80) ^a Reduce in decrements of 5	Consider changing to AC mode if there is high work of breathing with unassisted breaths
Assist/control	Term	Height of disease Weaning	Backup rate 30–40 Backup rate to remain below spontaneous breathing rate	Ensure as many inflations as possible are triggered
	Preterm	Height of disease Weaning	Backup rate 40–60 Backup rate to remain below spontaneous breathing rate	Ensure as many inflations as possible are triggered

SIMV synchronised intermittent mandatory ventilation, *AC* assist/control

^aStarting point (range)

tal evidence would suggest that it is better to apply sufficient PEEP at the airway opening rather than rely on the generation of an unknown and variable amount of inadvertent PEEP to improve lung volume (Yanos et al. 1998). Avoidance of dynamic hyperinflation is thus an important goal of neonatal ventilation, in particular in the context of an increased resistance to airflow. The flow waveform should be examined to ensure there is sufficient expiratory time for complete exhalation. A more definitive test for measurement of inadvertent PEEP has been described, which involves insertion of a T-piece in the ventilator circuit, brief interruption of ventilation by clamping and measurement of equilibrium pressure distal to the clamp (Simbruner 1986). If there is suspicion of incomplete exhalation, available options to prolong expiratory time include (a) reduction of ventilator rate with T_I kept constant or (b) shortening of T_I , if appropriate, whilst keeping ventilator rate constant. A combination of both of these may be the best solution.

42.4.5 Fractional Inspired Oxygen Concentration

Oxygen was first administered to newborns within 6 years of its discovery in 1774, and its administration to the premature neonate has con-

tinued in various forms thereafter (Silverman 2004). Use of “liberal” oxygen therapy, with an FiO_2 above 0.5, first became widespread in preterm infants in the late 1940s, and its impact on the developing retinal vasculature was soon apparent in the form of a large number of infants (more than 10,000) blinded by retinopathy of prematurity (Silverman 2004; Askie et al. 2009). In the aftermath of this disaster of iatrogenesis, there was the recognition of the need to restrict oxygen therapy (Askie et al. 2009), with measurement of both the FiO_2 and the oxygenation response of the infant now considered essential. Unrestricted and/or inadequately regulated oxygen therapy, and the retinopathy following from it, is now a significant concern in developing and newly industrialised countries (Gilbert 2008; Maida et al. 2008), and a “third epidemic” of retinopathy has emerged in these nations coincident with the increase in preterm survivors (Gilbert 2008; Maida et al. 2008).

Notwithstanding the above, titration of FiO_2 remains arguably the most neglected and least precise element of neonatal ventilation. Indwelling arterial oxygen sensors are no longer in use, and pO_2 readings in blood taken from an arterial line give only a snapshot in time. For this reason, moment by moment adjustments in FiO_2 are usually made on the basis of SpO_2 readings,

and it is clear that many infants, in particular pre-term infants, spend considerable amounts of time with SpO₂ readings (and therefore PaO₂ levels) outside the desired or target range (Hagadorn et al. 2006; Laptook et al. 2006; Claire et al. 2011). Given the shortages of nursing personnel in many neonatal units, very significant changes in SpO₂ may go unnoticed and uncorrected for some time, putting a patient at risk of the effects of hypoxia or hyperoxia (Claire et al. 2011; Bolivar et al. 1995). Automated control of FiO₂, discussed elsewhere in this text, offers the possibility of better targeting of SpO₂ ranges and less hyperoxia (Claire et al. 2011) but remains largely unavailable at present.

Frequent adjustments to FiO₂ are required in many ventilated newborns, in particular those with episodes of frequent apnoea or chest splinting in expiration (Bolivar et al. 1995). Prolonged periods of high FiO₂ may be necessary in infants with very significant parenchymal disease, pulmonary hypertension or both. In general, every opportunity should be taken to reduce FiO₂, both by choosing the lowest acceptable SpO₂ target and by optimising lung volume and recruitment at every juncture.

42.5 Acceptable Oxygen Saturation in Premature Infants

Oxygen saturation monitoring has been a routine part of neonatal intensive care for several decades, but until recently there has been a dearth of information concerning the correct target ranges (upper and lower limits) for SpO₂ in preterm infants receiving supplemental oxygen. In recent years, however, there has been an accumulation of clinical trial evidence regarding oxygen therapy and appropriate oxygen saturation targets in premature infants (STOP-ROP Multicenter Study Group 2000; Askie et al. 2003; Carlo et al. 2010; Schmidt et al. 2013; Stenson et al. 2013; Stenson 2013), overcoming at least in part a great deal of uncertainty (Tin and Wariyar 2002). This information has been taken into account in formulating the recommendations for SpO₂ target ranges indicated in Table 42.7.

Table 42.7 Suggested target ranges for oxygen saturation

<i>Preterm < 28 weeks gestation at birth</i>	
Before 36 weeks CGA ^a	90–94 %
≥36 weeks CGA	92–96 %
<i>Preterm 28–36 weeks gestation at birth</i>	
Before 36 weeks CGA	90–94 %
≥36 weeks CGA	92–96 %
<i>Term</i>	
Parenchymal lung disease	92–96 %
Persistent pulmonary hypertension	94–98 % ^a
Cyanotic congenital heart disease	70–85 % ^b

CGA corrected gestational age
^aAppropriate pO₂ target at least 50 mmHg
^bWhere there is a duct-dependent pulmonary blood flow, supplemental oxygen may constrict or close the ductus arteriosus

42.5.1 What Is the Safe Upper Limit for SpO₂ in the Preterm Infant?

The association of hyperoxia with adverse pulmonary, neurological and retinal effects in the pre-term infant is well understood and is discussed elsewhere in this book. In the era of saturation monitoring, relative hyperoxia (SpO₂ ≥95 %) from 32 weeks corrected gestation or beyond has been associated with progression of chronic lung disease (STOP-ROP Multicenter Study Group 2000; Askie et al. 2003), without altering the outcome of retinopathy (STOP-ROP Multicenter Study Group 2000). More recently, a number of clinical trials, conducted in the USA, Canada, UK, Australia and New Zealand, have compared target SpO₂ ranges of 85–89 % and 91–95 % commenced soon after birth in preterm infants <28 weeks gestation. These target ranges remained in force up until 36 weeks corrected gestation, as long as the infant is receiving supplemental oxygen. An initial report from each of these studies has now been published (Carlo et al. 2010; Schmidt et al. 2013; Stenson et al. 2013), and an individual patient meta-analysis combining data from all trials (the NeOProM collaboration) is awaited (Stenson 2013). Three methodological issues in these trials bear consideration. The first is that for both high (91–95 %) and low (85–89 %) target groups, the actual SpO₂ readings when in supplemental oxygen were at the high end of the

intended range, likely a reflection of a well-documented tendency for bedside staff to target the high end of an SpO₂ range (Clucas et al. 2007). Moreover, the upward shift in actual SpO₂ readings was more prominent in the lower target group, with a median SpO₂ value of around 90–91 %, and on average only a 3 % separation between readings in the two groups, rather than the 6 % that would have been expected. The second methodological consideration is that while the trials were being conducted, the SpO₂ calibration curve within the oximeters being used was found to under-represent SpO₂ values of 87–90 % (Stenson 2013). Installation of a revised algorithm in the UK and Australian trials led in to a clearer separation in SpO₂ readings between the groups, and appeared to affect the outcomes (see below). The final methodological issue is that in only one of the studies (the COT study, Schmidt et al. 2013) were both upper and lower alarms limits clearly stipulated and enforced, which may have affected the proportion of extreme SpO₂ values, and thus potentially the results.

Overall the findings of the recent clinical trials of SpO₂ targeting were (a) that a lower target range (85–89 %) was associated with an increased risk of mortality (the exception being the COT study (Schmidt et al. 2013)), with the relative risk of in-hospital mortality being 1.3 to 1.4 (Carlo et al. 2010; Stenson et al. 2013); (b) that a lower target range also appeared to predispose to necrotising enterocolitis; and (c) that a higher target range (91–95 %) was associated with an increase in retinopathy of prematurity (relative risk 1.3–2.0) with again the COT study being the exception. The COT study investigators commented that strict enforcement of alarm limits, and in particular the upper limit, may have contributed to the lack of association between the high target group and retinopathy noted in their study.

The SpO₂ targeting trials performed to date have not examined multiple SpO₂ ranges, and thus recommendations about the safe upper and lower limits can only be based on the information at hand. Nevertheless, balancing the risks of mortality and necrotising enterocolitis on the one hand, against the risk of retinopathy on the other, an upper SpO₂ limit of 94 % would seem

prudent, with an alarm set at 96 % and active at all times when in supplemental oxygen (Table 42.7). A higher upper limit (96 %) is appropriate for preterm infants beyond 36 weeks corrected gestation. The upper limit of 96 % can also be applied from the outset to term infants with parenchymal lung disease, in whom the risk of retinopathy is negligible. A higher target range (and thus upper limit) is recommended for infants with pulmonary hypertension (Table 42.7).

42.5.2 What Is the Safe Lower Limit for SpO₂ in the Preterm Infant?

The combined results of the SpO₂ targeting trials point to an increase in mortality and probably necrotising enterocolitis where an SpO₂ below 90 % is targeted. For this reason, a lower SpO₂ limit at or above 90 % has been recommended for preterm infants <36 weeks corrected age (Table 42.7). A lower SpO₂ limit at or above 92 % is appropriate for term infants in most clinical contexts (Table 42.7), with the exception being cyanotic congenital heart disease.

42.6 Safe CO₂ Limits

There are good experimental data in support of the role of permissive hypercapnia in lung injury protection (as discussed elsewhere in this book). These effects go beyond the reduced minute ventilation that goes hand in hand with permissive hypercapnia; elevated FiCO₂ appears to offer protection independent of minute ventilation (Peltekova et al. 2010). The need for lower minute ventilation should in itself reduce lung injury in the preterm infant, although this hypothesis, whilst supported in a small single-centre trial (Mariani et al. 1999), was not clearly validated in the large clinical trial conducted by the Neonatal Research Network (Carlo et al. 2002).

The safe limits of PaCO₂ are difficult to determine from available literature. Despite decades of use of mechanical ventilation of newborn infants,

the number and quality of studies specifically addressing this critical question is surprisingly low. There is unequivocal evidence that low PaCO_2 is associated with increased risk of severe intraventricular haemorrhage (IVH) and periventricular leukomalacia (Graziani et al. 1992; Fujimoto et al. 1994; Wiswell et al. 1996; Okumura et al. 2001; Collins et al. 2001) and that very high levels, especially in preterm infants during the first few days of life, may also increase the risk of IVH (Kaiser et al. 2006; Fabres et al. 2007). The data of Fabres et al. indicated that even modestly decreased PaCO_2 (<39 mmHg) was associated with a twofold increase in IVH, as was a maximal PaCO_2 over 60 mmHg and prolonged exposure to a PaCO_2 greater than 52 mmHg. However, safe lower and upper limits remain an open question. The postnatal age of the infant, the degree of prematurity and coexisting morbidities, such as asphyxia, hypotension and sepsis, which are known to impair cerebral blood flow autoregulation, all affect the vulnerability of the patient to high or low levels of CO_2 . The studies showing association of hypercapnia and IVH focussed on the early postnatal period. The only large prospective clinical trial of permissive hypercapnia suggests safety of mild permissive hypercapnia, but the mean PaCO_2 remained between 45 and 50 mmHg for the first 7 days of life in the "hypercapnia" group (Carlo et al. 2002). This study does not, therefore, refute the retrospective data suggesting increased risk of adverse outcomes with maximal PaCO_2 values above 60 mmHg during the first week of life (Fabres et al. 2007). Whilst there are very plausible pathophysiological mechanisms which link hypercapnia to IVH, it must be recognised that the retrospective studies cannot establish causation. It is possible that high CO_2 values are a marker for other events or a reflection of the severity of illness rather than the cause of the IVH. A relatively small prospective trial targeting PaCO_2 values between 55 and 65 from birth enrolled only one-third of the projected sample size (65 infants) before being stopped early because target PCO_2 values could not be reached (Thome et al. 2006). This study found no difference in pulmonary outcomes but an increase in the composite outcome of death or neurological impairment at 18–22 months from 42 to 62 % in

the hypercapnia group, despite a difference of only 6 mmHg in PaCO_2 values between the groups.

Data on safety of permissive hypercapnia beyond the first week of life are lacking. It is generally believed that because of metabolic compensation and less vulnerability to IVH, higher levels of PaCO_2 can be tolerated safely, but neither the validity of the assumption nor the safe upper limits of PaCO_2 during this period have been established.

Although clinical studies have focussed on PaCO_2 , whether PaCO_2 or pH should be our primary concern is still subject to debate; clinical studies have not specifically addressed the question of whether compensated respiratory acidosis is safe or whether the infant with metabolic acidosis compensated by hyperventilation is at similar risk as one who has an uncompensated alkalosis. Experimental studies clearly show, however, that local tissue pH, not pCO_2 , is the primary determinant of cerebral vasoconstriction or dilatation (Fencl et al. 1968; Kontos et al. 1977). Rapid changes in PaCO_2 are also dangerous and should be avoided, because they lead to rapid changes in cerebral blood flow (Raichle et al. 1970; Gleason et al. 1989). A large retrospective study of 849 preterm infants concluded that not only both extremes of CO_2 but also fluctuations in PaCO_2 are associated with severe IVH (Fabres et al. 2007).

What then is the clinician to do in the face of such uncertainty? First, it should be recognised that low PaCO_2 values are clearly more dangerous than moderately high values and that targeting mildly hypercapnic values decreases the risk of inadvertent hypocapnia. Second, it is important to avoid rapid changes in PaCO_2 . On balance, available evidence suggests that keeping PaCO_2 values in the range of 45–50 mmHg during the first week of life is appropriate and safe. As a practical matter, because very preterm infants have a low renal threshold for bicarbonate and tend to have a modest metabolic acidosis, it is difficult to achieve significant hypercapnia during the first few days of life without unacceptable degree of acidosis. With time, the vulnerability of the brain to IVH decreases, and metabolic compensation develops, allowing PaCO_2 to rise to levels of 50–60 mmHg with relatively normal pH by the second and third

week of life. Permissive hypercapnia with PaCO₂ values of 60–70 mmHg is widely practised and not clearly associated with adverse outcomes. The safety of this approach is in need of urgent study.

Essentials to Remember

- Ventilator settings in the neonate should be individualised, taking into account the context in which respiratory failure has occurred, the effects on lung volume and compliance and the vulnerability of the lung to injury.
- Where possible, ventilation should be in synchrony with spontaneous respiratory effort.
- PEEP is the most important determinant of end-expiratory lung volume and oxygenation.
- Delivery of each tidal breath is important not only for gas exchange but also recruitment.
- Premature neonates are more vulnerable to oxygen toxicity, and the target SpO₂ range in these infants is thus lower than for term infants.
- Hypocapnia is significantly more dangerous than hypercapnia in ventilated neonates.

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Educational Aims

- Describe the process of selecting initial ventilator settings on initiation of invasive mechanical ventilation.
- Understand the various elements of invasive mechanical ventilation and their interaction with an individual patient's underlying pathophysiologic process(es).
- Discuss the importance of ventilator-induced lung injury as a consideration for selecting mechanical ventilator settings.

- Review the implications of invasive mechanical ventilation on specific disease processes in the pediatric critical care environment.
- Review the data (or lack thereof) to support various ventilatory strategies.

43.1 Introduction

The initiation of mechanical ventilation and selection of initial ventilator settings is a complex process that must address the underlying pathophysiology and the change in clinical status which may follow intubation and the implementation of positive pressure breathing. The initial ventilator settings must be instituted to target a patient's specific clinical indication(s) for mechanical ventilation. Due to the substantial variation in disease processes, no single ventilator strategy can be successfully applied to all patients. The strategy used for a patient with acute respiratory distress syndrome (ARDS) will vary greatly from that for status asthmaticus or a chronic neuromuscular disorder. An additional factor in the approach to mechanical ventilation in the pediatric critical care setting is the tremendous variation in both patient age and size. These considerations are important elements in the development of an approach to mechanical ventilation of the pediatric patient.

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Table 43.1 Suggested ventilator targets for lung protection

Conventional ventilator settings	Common pitfalls
Mode: Variable, decelerating inspiratory flow pattern is preferred to (a) optimize patient comfort and (b) augment mean airway pressure while minimizing peak inspiratory pressure Volume-limited or pressure-limited modes may be safely applied to pediatric patients	Applying adult settings to pediatric patients Excessively long inspiratory time and/or high set respiratory rates leading to “gas trapping” and intrinsic PEEP
Tidal volume: approximately 6 ml/kg ideal body weight for patients with acute lung injury; 6–10 ml/kg for pediatric patients with normal lungs	Overdistending healthy lungs with excessive tidal volume
Pressure: PIP < 30 cm H ₂ O PEEP to maintain an open-lung approach without adversely affecting hemodynamics	Overdistending healthy lungs with excessive airway pressure
FiO₂: strive to maintain $FiO_2 \leq 0.50$	Excessive oxygenation targets
Inspiratory time (T_i): Appropriate T_i (based on patient age/size): Optimize patient comfort Avoid air trapping Longer T_i may be needed to maintain higher mean airway pressure in patients with significant acute lung injury	Excessively long T_i in tachypneic patients, leading to air trapping and intrinsic PEEP
Clinical targets pH: Normal pH (7.35–7.45) if minimal ventilator settings Generally allow lower pH (7.20–7.30) in hemodynamically stable patients on increased ventilator settings; allow elevated PaCO ₂ (permissive hypercapnia), except in those patients with increased intracranial pressure or significant, reactive pulmonary hypertension	Over ventilating injured lungs to achieve normal pH
PaCO₂: Allow pH targets to dictate PaCO ₂ Consider disease-specific PaCO ₂ targets (e.g., pulmonary hypertension, traumatic brain injury)	Over ventilating injured lungs to achieve normal PaCO ₂
SpO₂: Wean oxygen to maintain normal oxygenation (generally SaO ₂ > 93 %) Tolerate SaO ₂ > approx. 85–88 % for patients with adequate oxygen delivery and requiring “toxic” ventilatory support (permissive hypoxemia)	Maintaining high levels of FiO ₂ to maintain supranormal SaO ₂

As decisions are made regarding mechanical ventilation, the clinician must always consider the principle of *non-maleficence*, which dictates that we must first not harm our patients. More specifically, attention should be paid to lung-protective ventilation from the outset of mechanical ventilation. Even brief periods of positive pressure ventilation can damage lung. Ventilator-induced lung injury (VILI) generally increases as critical illness worsens and higher levels of ventilatory support are employed (Vitali and Arnold 2005). Clinical studies have demonstrated relatively safe targets for ventilation as discussed below (Table 43.1) (Cheifetz 2003; The Acute Respiratory Distress Syndrome Network 2000;

Arnold et al. 2000; Dahlem et al. 2007; Kissoon et al. 2008; Laffey et al. 2004; Mesiano and Davis 2008; Rotta and Steinhorn 2006, 2007).

It should be noted that there are circumstances in which invasive mechanical ventilation may be avoided by the utilization of noninvasive ventilation (NIV) as discussed elsewhere in this textbook. Even in the setting of acute lung injury (ALI) and ARDS, patients may be effectively and successfully treated with NIV. However, the use of NIV in infants and children can be complicated by difficulties with both the patient interface and patient cooperation, thus, potentially necessitating intubation and invasive support. The focus of this chapter is on the processes and

considerations surrounding implementation of invasive mechanical ventilation in the pediatric critical care environment.

43.2 Mode of Invasive Mechanical Ventilation

The key to an optimal approach to invasive mechanical ventilation is matching the advantages/disadvantages of a specific ventilatory mode to an individual patient's pathophysiology. From the start, it must be stressed that no clinical neonatal or pediatric study has definitively demonstrated that any one mode is more beneficial than another in improving outcomes, except for high-frequency ventilation in the setting of neonatal respiratory distress syndrome in which the incidence of chronic lung disease is reduced (Campbell and Davis 2002; Branson and Johannigman 2004; Fan et al. 2005; Ortiz 2010; Maxwell et al. 2010; Duyndam et al. 2011; González et al. 2010; Cools et al. 2009; Hofhuis et al. 2002).

Conventional mechanical ventilation includes three general mode types: assist control (e.g., pressure control ventilation), support (e.g., pressure support ventilation), and mixed (e.g., synchronized intermittent mandatory ventilation (SIMV) plus pressure support). No data exist to support the superiority of any of these approaches, and advantages and disadvantages of each type of mode can be debated (Campbell and Davis 2002; Branson and Johannigman 2004; Fan et al. 2005; Ortiz 2010; Maxwell et al. 2010; Duyndam et al. 2011; González et al. 2010).

A control mode is defined by a clinician-set inspiratory time, while a support mode is defined by a patient-determined inspiratory time. Control modes are occasionally used in the Pediatric ICU, but most pediatric patients prefer an inspiratory time (T_i) shorter than generally chosen by the clinician. These patients, therefore, tend to be more comfortable in a support mode (i.e., patient-controlled T_i) (Banner et al. 1991). However, pediatric patients, especially infants, may become significantly tachypneic in a support mode, further decreasing T_i and subsequently decreasing

mean airway pressure (P_{AW}). As P_{AW} falls, this clinical scenario may lead to atelectasis and a subsequent need for increasing positive end-expiratory pressure (PEEP). One approach to the use of support modes (e.g., pressure support ventilation) in infants is to set the PEEP at approximately 2 cm H₂O above the lower inflection point to maintain the P_{AW} in the event that the patient's intrinsic inspiratory time were to decrease.

Alternatively, a mixed control/support mode may be utilized. With such an approach, the support breaths improve patient comfort, while a set rate of controlled breaths with a longer T_i helps to maintain mean airway pressure and lung recruitment. A key consideration in this context is to set T_i for the control breaths relative to the baseline respiratory rate, to allow for adequate expiratory time. The maintenance of adequate expiratory time in this manner avoids air trapping and the development of intrinsic PEEP. It should be stressed that with the lack of definitive data supporting one mode over another, the choice of ventilatory mode is often left to institutional bias and individual clinical choice. The mode chosen for a given patient should be based on the patient's pathophysiology, keeping in mind that this may change over time.

In an attempt to optimize patient-ventilator synchrony and minimize pharmacologic sedation, several manufacturers have developed novel approaches to conventional mechanical ventilation. Increasing emphasis is being placed on spontaneous breathing and its potential benefits in the management of acute respiratory failure. Such modes include proportional assist ventilation (PAV), neurally adjusted ventilatory assist (NAVA), and adaptive support ventilation (ASV) (Beck et al. 2007; Colombo et al. 2008; Schmidt et al. 2010; Spahija et al. 2010; Terzi et al. 2010; Sinderby et al. 2007; Barwing et al. 2009; Coisel et al. 2010; Alander et al. 2012; Bengtsson and Edberg 2010; Younes 1992; Kacmarek 2011; Giannouli 1999; Kondili et al. 2006; Wrigge et al. 1999; Xirouchaki et al. 2008). These non-traditional approaches are designed to share the ventilating pressure between patient and ventilator to proportionally unload respiratory effort

and, thus, theoretically improve synchrony. In these modes of ventilation, the patient maintains control of the ventilatory pattern. From a physiologic basis, this approach both makes sense and is supported by several relatively small studies; however, definitive outcome data are lacking (Beck et al. 2007; Colombo et al. 2008; Schmidt et al. 2010; Spahija et al. 2010; Terzi et al. 2010; Sinderby et al. 2007; Barwing et al. 2009; Coisel et al. 2010; Alander et al. 2012; Bengtsson and Edberg 2010; Younes 1992; Kacmarek 2011; Giannouli 1999; Kondili et al. 2006; Wrigge et al. 1999; Xirouchaki et al. 2008). A comprehensive review of these novel approaches to pediatric mechanical ventilation is beyond the scope of this chapter.

When appropriate clinical targets cannot be achieved with “safe” conventional ventilator settings using the more traditional modes, providers must consider alternative forms of ventilation. High-frequency oscillatory ventilation (HFOV), high-frequency jet ventilation (HFJV), high-frequency percussive ventilation (HFPV), and airway pressure release ventilation (APRV) usually improve oxygenation and/or ventilation, presumably, in a more lung-protective manner.

Each of these modes has advantages and disadvantages, which should be considered when choosing a ventilation strategy. APRV allows spontaneous ventilation throughout the ventilatory cycle and, thus, would be expected to require reduced sedation and neuromuscular blockade requirements as compared to other modalities (Maxwell et al. 2010; Duyndam et al. 2011; González et al. 2010). Although APRV offers an attractive strategy for the pediatric patient with acute lung injury, it has not seen widespread application. Additionally, outcome data have not proven this to be a beneficial approach as compared to more conventional approaches (Maxwell et al. 2010; Duyndam et al. 2011; González et al. 2010; Maung et al. 2012).

HFOV functions at an elevated mean airway pressure with an attenuated pressure amplitude at the alveolar level to augment oxygenation while providing lung-protective ventilation. HFOV has become a standard approach in many neonatal and pediatric intensive care units, although definitive

outcome data in the pediatric population remain lacking (Arnold et al. 2000). HFJV is limited to the neonatal and infant population due to the technical limitations of the device (i.e., patient size limitations). The key advantage of HFJV is its continuous passive exhalation, an extremely efficient approach to carbon dioxide elimination (Meliones et al. 1991; Musk et al. 2011; Bunnell 2001). In the small pediatric population, HFJV is most helpful in those patients with pulmonary hypertension in which the partial pressure of carbon dioxide must be closely controlled and/or those patients with acute lung injury in whom permissive hypercapnia would not be acceptable. Lastly, HFPV provides the additional benefit of enhancing secretion removal while improving oxygenation and/or ventilation and providing a lung-protective approach to patient management.

Clinical targets using these modes of ventilation should include both permissive hypercapnia and permissive hypoxia (Arnold et al. 2000; Rotta and Steinhorn 2006; Kavanagh et al. 2006; Peltekova et al. 2010; Cheifetz and Hamel 2006; Cheifetz 2011a; Abdelsalam and Cheifetz 2010) as clinically indicated and remain generally the same as with conventional ventilation as discussed elsewhere in this text. If the patient continues to deteriorate despite “maximal” ventilatory support, extracorporeal membrane oxygenation (ECMO) should be considered for refractory respiratory failure.

43.3 Tidal Volume

In adult patients with acute lung injury, maintaining the tidal volume at 6 ml/kg of ideal body weight (IBW) and maintaining the plateau pressure less than 30 cm H₂O significantly reduced mortality when compared with a higher tidal volume strategy of 12 ml/kg IBW (The Acute Respiratory Distress Syndrome Network 2000). This study controlled for both plateau pressure and delivered tidal volume, and despite multiple additional clinical trials, it remains controversial whether lung overdistension (i.e., volutrauma) or excessive pressure (i.e., barotrauma) is more damaging to the lung. It is most likely that both

pressure and volume in combination play a significant role in VILI. As pressure and volume are intrinsically linked by compliance, the same strategies that limit one will generally limit the other.

Extrapolating these adult data to children with acute lung injury, it is likely safe to target a tidal volume of 6 ml/kg IBW while keeping the peak inspiratory pressure less than 30 cm H₂O. However, it must be stressed that definitive pediatric data are lacking. With the increasing prevalence of obesity in the pediatric population, it is important to stress that these tidal volume calculations must be performed on ideal, rather than actual, body weight (Cheifetz 2011a, b).

If tidal volume targets are maintained and appropriately monitored, different modes of ventilation (i.e., volume-limited vs. pressure-limited) should be equivalent. Either mode can usually deliver the same sized mechanical breaths without substantial differences, and there are no data to suggest one modality is superior to another. It should again be stressed that the specific mode is much less important than the clinical management of the mode based on the physiology and the clinician-set ventilator parameters.

Another important variable which must be considered when setting tidal volume is the location of the tidal volume measurements. The tidal volume set (or measured) on the ventilator may be significantly higher than the tidal volume a patient's lungs actually receive (referred to as the delivered or effective tidal volume) (MacIntyre 1990; Tobin 1992; Cannon et al. 2000). This difference is a result of the compressible volume of gas in the ventilator circuit and is magnified in neonates and small infants as the quantity of compressible gas is a relatively larger percent of the ventilator-delivered tidal volume (Cannon et al. 2000; Binda et al. 1976; Epstein 1971; Haddad and Richards 1968; Martin et al. 1989; Castle et al. 2002; Chow et al. 2002; Heulitt et al. 2009).

Thus, accurate monitoring of tidal volume can be difficult in neonates, infants, and small children. Expiratory valve measurements, on average, may be 44 % higher for neonatal circuits and 27 % higher for pediatric circuits than the tidal

volume measured at the endotracheal tube (Cannon et al. 2000). These inaccuracies are due to both a larger circuit dead space to tidal volume ratio and a greater effect of circuit compliance on tidal volume measurement. Some mechanical ventilators employ a calculation to estimate the effective delivered tidal volume taking into account the compliance of the ventilator circuit. However, such calculations may be affected by changes in the compliance of the ventilator circuit over time (e.g., temperature variations, secretions, circuit adaptors).

For these reasons, it has been recommended that the actual tidal volume delivery be monitored and managed using a pneumotachometer placed between the endotracheal tube and ventilator circuit (Cannon et al. 2000; Castle et al. 2002; Chow et al. 2002; Heulitt et al. 2009). Measuring exhaled tidal volume at the endotracheal tube leads to a more accurate determination of the actual tidal volume delivered to a small pediatric patient's lungs, allowing providers to better prescribe tidal volume and subsequently follow a lung-protective strategy.

43.4 Positive End-Expiratory Pressure

The application of PEEP is an essential step in providing respiratory support for mechanically ventilated patients of all ages (Dantzker et al. 1979; Pontoppidan et al. 1972a, b, c). If set appropriately, PEEP helps to maintain an appropriate lung volume, minimize atelectasis, improve ventilation/perfusion matching, and reduce right-to-left intrapulmonary shunting (Hammon et al. 1976; Suter et al. 1975; Tyler 1983). Determining "optimal" PEEP remains a clinical challenge. Several methods may be employed to set the "best" PEEP for an individual patient. One approach is to use pressure-volume curves to set the PEEP at approximately 2–3 cm H₂O above the lower inflection point (Fig. 43.1). Once the lungs are recruited using this method, clinicians should then wean the PEEP to the minimal value needed to keep the lung open, while closely monitoring the pressure-volume curve. Another

method of PEEP titration involves the use of PEEP-FiO₂ tables. Unfortunately, generally accepted PEEP-FiO₂ tables are only available for the adult population.

As a general PEEP titration approach, as modeled in Table 43.2, providers may vary PEEP in a stepwise fashion to determine which level of PEEP best optimizes a range of clinically relevant markers. This method of PEEP titration can be important for patients with multiorgan dysfunction in that it considers the effects of PEEP on oxygen delivery and cardiac function. While the impact on nonpulmonary organs and overall oxygen delivery is an important consideration, unfortunately, cardiac output remains challenging to accurately measure in pediatrics. In children and neonates, surrogate measures of oxygen delivery must often be substituted to estimate the impact of PEEP titration. The ultimate goal is to find the “best” PEEP for a given patient that optimizes pulmonary compliance and global oxygen delivery (i.e., the best balance between lung

volume, cardiac output, and global arterial oxygen delivery).

Regardless of the method chosen, an important consideration in setting PEEP is the principle of hysteresis. Hysteresis demonstrates that more energy is required to open the lungs than to maintain lungs open. VILI is worsened by the atelectrauma created by the cycle of alveolar collapse and reopening created by inadequate end-expiratory pressure. Once atelectasis develops, additional energy, delivered in the form of increased airway pressure, is required to reopen the alveoli (Prodhan and Noviski 2004). This need for increased pressure to overcome alveolar collapse exacerbates VILI.

Adequate PEEP and open-lung strategies attempt to maintain appropriate lung inflation during exhalation to maintain the alveoli in their phase of optimal compliance and, hopefully, to avoid (or at least minimize) iatrogenic lung injury (Rimensberger 2009). An additional approach to the prevention of atelectrauma is the use of recruitment or sustained inflation maneuvers. While their use remains controversial in both the pediatric and adult populations, carefully performed lung recruitment maneuvers may be safely used to achieve an open-lung state (Prodhan and Noviski 2004; Turner and Arnold 2007). It should be noted that careful attention must be paid to avoiding pulmonary hyperinflation during recruitment maneuvers and PEEP titration. One mechanism to monitor for hyperinflation/overdistension is the pressure-volume loop (Fig. 43.1). These loops can alert providers of hyperinflation through the presence of decreasing compliance, “beaking,” and an upper inflection point. Careful clinical monitoring is crucial as PEEP is adjusted while balancing optimal lung inflation with the risk of VILI.

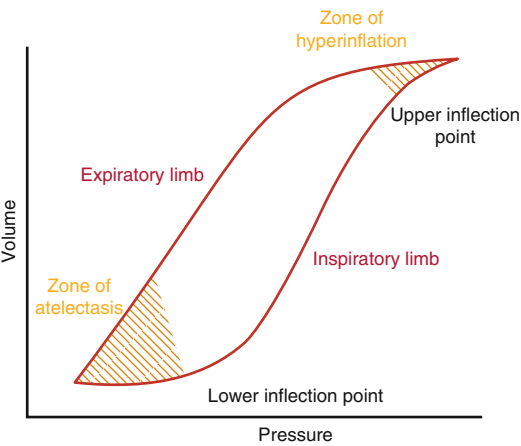


Fig. 43.1 Pressure-Volume curve of the lung

Table 43.2
Sample PEEP
table

	PEEP=6	PEEP=9	PEEP=12	PEEP=15
Lung expansion	Atelectatic	Atelectatic	Ideal	Hyperinflated
Pulmonary vascular resistance	++	+	–	+
Cardiac output	++	+	No change	--
Oxygenation	--	–	+	++
Intracranial pressure	--	+/-	+/-	++
Oxygen delivery	–	+/-	+	–

43.5 Inspiratory Flow Pattern

The choice of inspiratory flow pattern has an impact on ventilatory mode selection and often depends on the specific ventilator(s) available. There may be several options for inspiratory flow pattern, but in most situations, inspiratory flow is either constant or decelerating. With a constant inspiratory flow pattern, a “square wave” is produced by the constant flow of gas throughout the inspiratory cycle. In many clinical scenarios, this flow pattern may be associated with less comfortable spontaneous respiratory effort and increased patient-ventilator dyssynchrony.

In contrast, a variable inspiratory flow pattern generally provides the maximal flow near the onset of inspiration with flow then decreasing at a variable rate throughout the remainder of inspiration. This variable, decelerating flow pattern is generally preferred over a constant flow pattern in most patients as it is a more natural inspiratory breathing pattern that provides sustained mean airway pressure with a lower peak inspiratory pressure when compared to constant flow (Fig. 43.2) (Cinnella et al. 1996; Wong et al. 2000). This pattern maximizes P_{AW} with lower peak inspiratory pressures, allowing clinicians to achieve oxygenation goals with potentially less risk for VILI (Cheifetz 2003). In addition, the more natural breathing pattern of decelerating flow would be expected to lead to better patient-ventilator synchrony, which may in turn decrease sedation requirements.

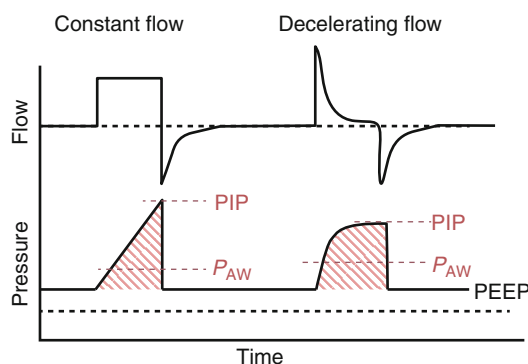


Fig. 43.2 Flow and Pressure vs. Time Scalars comparing constant versus decelerating inspiratory flow patterns

43.6 Triggering

Setting ventilator trigger for infants and children can be challenging given the variation in size and disease processes. Many infants and small children have difficulty triggering ventilators because of their relatively weak respiratory musculature. Thus, flow triggering is generally preferred to pressure triggering.

Flow triggers allow for increased ventilator sensitivity in situations where small patients are unable to generate adequate pressure to trigger the ventilator. A small subset of the weakest infants may require flow triggers less than 0.5 l/min. However, auto-triggering can become a risk, especially in the setting of leaks around the endotracheal tube. While becoming less common, uncuffed endotracheal tubes are still frequently utilized in a wide range of clinical scenarios, and the air leak around these tubes can be quite variable. Patients with large air leaks may require higher flow triggers (up to 2.0 l/min) to maintain clinical targets and achieve gas exchange goals without autocycling.

43.7 Inspired Oxygen Concentration

While oxygen is required by the body for cellular respiration and metabolism, elevated levels can have damaging effects on the lung by producing free radicals and reactive oxygen species (Vento et al. 2009; Yee et al. 2009; Frank et al. 1978; Carvalho et al. 1998). The toxicity of high levels of inspired oxygen can lead to direct damage to cell membranes, cellular proteins, and DNA, thus, leading to cell necrosis, apoptosis, and further inflammation (Auten and Davis 2009). Minimizing FiO_2 in the setting of mechanical ventilation is an important consideration, and there are limited data to suggest that an FiO_2 less than 0.50 will ameliorate the toxic effects (Dos Santos 2007). However, increased ventilator settings (e.g., mean airway pressure) may be necessary to decrease the FiO_2 . In patients with refractory hypoxemia, substantial increases in ventilatory support may be needed, and the

balance between oxygen toxicity and potential VILI may become increasingly difficult to manage.

43.8 Ventilatory Frequency

In infants and children, the normal physiologic respiratory rate varies significantly depending on patient age. The patient's expected physiologic rate should largely dictate the set ventilatory frequency. As a general guideline, deviation from normal physiologic respiratory patterns with regard to rate and inspiratory time should be avoided.

When spontaneous or mixed modes of ventilation are utilized, the frequency may be set below the patient's physiologic rate, allowing the patient to breathe above the set minimum (or backup) rate. In clinical scenarios in which the predominant pathophysiology is prolonged expiration (i.e., asthma, bronchiolitis), it is often required that the respiratory frequency be decreased to avoid premature termination of exhalation and gas trapping (i.e., auto-PEEP or intrinsic PEEP). Gradually decreasing the set frequency with an increased dependence on spontaneous ventilatory effort is often used as an approach to ventilator weaning.

In contrast, an increase in respiratory frequency above the "normal" physiologic rate is rarely necessary unless hyperventilation is a specific clinical goal. Therapeutic hyperventilation may be necessary in certain clinical circumstances, and refractory respiratory acidosis may also necessitate an increased ventilator frequency. When increased frequency is necessary to achieve clinical endpoints, close monitoring and analysis of airway graphics are necessary to prevent inadvertent inverse ratio ventilation or "gas trapping."

43.9 Inspiratory Time

Inspiratory time is generally set at 0.40–0.65 s in infants, 0.5–0.75 s in children, and 0.7–1.0 s in adolescents. Inspiratory time is generally not

reduced below approximately 0.40 s in the pediatric critical care environment due to the possibility that shorter times may not allow adequate time for the distribution of gas to the alveolar units. It is important for the bedside clinician to monitor the flow-time scalar to ensure that expiratory flow returns to baseline (i.e., zero flow) prior to the initiation of the next breath. Such an approach will avoid the occurrence of gas trapping and intrinsic PEEP.

Inspiratory time may be increased to augment P_{AW} and improve oxygenation, but prolongation of the inspiratory time may result in an excessively high inspiratory-to-expiratory ratio and "gas trapping." An excessive prolongation of inspiratory time can also result in significant elevations in the P_{AW} resulting in an impedance to systemic venous return, a reduction of right ventricular filling, and a resultant decrease in cardiac output (Cournand et al. 1948). Historically, a prolongation of the inspiratory time in this manner with an increased, or reversed, inspiratory/expiratory ratio had been advocated as a means of increasing P_{AW} and recruiting low ventilation/perfusion compartments in diseases involving decreased compliance and lung volumes (Reynolds and Taghizadeh 1974). More recently, the use of APRV has provided for significant elevations in the mean airway pressure, while still allowing spontaneous ventilation and avoiding gas trapping.

43.10 Gas Exchange Parameters and Assessing the Adequacy of Mechanical Ventilation

There are obviously a wide range of indications for intubation and invasive ventilation. Regardless of the indication for mechanical support, once a patient is successfully transitioned to the ventilator and stabilized, targets must be established to guide titration of the level of ventilatory support. Specific indications for invasive mechanical ventilation and gas exchange parameters are discussed in detail elsewhere in this textbook. The ultimate goal is to establish adequate oxygen delivery to the organs and tissues

throughout the body. The gas exchange targets for an individual patient must be tailored to the specific physiology, pathophysiology, and severity of illness.

Prevention of VILI is a crucial consideration in the titration of mechanical ventilation. In some circumstances, patients may become refractory to escalating levels of support, necessitating the acceptance of suboptimal clinical targets to prevent further VILI. Depending on the disease process(es), providers must decide if a patient will tolerate lower pH, higher $p\text{CO}_2$, and/or lower oxygen saturations than generally targeted (Table 43.1). These concepts are termed permissive hypercapnia and permissive hypoxemia (Arnold et al. 2000; Rotta and Steinhorn 2006; Kavanagh et al. 2006; Peltekova et al. 2010; Cheifetz and Hamel 2006; Cheifetz 2011a; Abdelsalam and Cheifetz 2010).

It is important to note that the level of ventilatory support required to achieve normalization of pH and $p\text{CO}_2$ may induce secondary ventilatory lung injury. Permissive hypercapnia is a strategy in which $p\text{CO}_2$ is allowed to rise to minimize VILI. Studies have demonstrated that this approach is safe, and some experts have demonstrated that elevated $p\text{CO}_2$ may attenuate lung injury (Laffey et al. 2004). Permissive hypercapnia is often used in the setting of severe respiratory failure, although no definitive studies exist to address the short- or long-term impact of elevated $p\text{CO}_2$ and lower pH in infants and children.

An arterial pH of >7.20 is considered acceptable by many, but even lower pH thresholds may become necessary in the setting of significant lung injury requiring toxic ventilatory support (Arnold et al. 2000; Rotta and Steinhorn 2006; Kavanagh et al. 2006; Peltekova et al. 2010; Cheifetz and Hamel 2006; Cheifetz 2011a; Abdelsalam and Cheifetz 2010). Most hemodynamically stable patients will tolerate this approach; however, careful consideration must be given to those patients with significant intracranial pathology, pulmonary hypertension, and/or myocardial dysfunction (Kavanagh et al. 2006; Peltekova et al. 2010). Most would consider intracranial hypertension a contraindication to permissive hypercapnia.

The control of $p\text{CO}_2$ and pH is intimately linked to the titration of tidal volume and inspiratory pressure. In adults with acute lung injury, an approach that limited both tidal volume (6 ml/kg) and plateau pressure (<30 cm H_2O) improved mortality (The Acute Respiratory Distress Syndrome Network 2000). The relative contribution to this mortality benefit of tidal volume versus plateau pressure remains unclear. Limitation of both of these parameters has become generally (but not universally) accepted in the management of pediatric acute lung injury. Definitive data and the optimal limits for tidal volume and plateau pressure remain lacking for infants and children (Albuali et al. 2007).

Similarly, most patients with adequate cardiac output and acceptable hemodynamics will tolerate permissive hypoxia (Cheifetz and Hamel 2006; Abdelsalam and Cheifetz 2010). The minimal acceptable oxygen saturation goal must be individualized to each patient's pathophysiology, overall clinical status, and degree of ventilator support required. With this strategy, oxygen saturations are allowed to decrease in those with severe ARDS in an attempt to avoid exposing the lungs to high levels of FiO_2 and toxic ventilator support (Cheifetz and Hamel 2006; Abdelsalam and Cheifetz 2010). The lower limit of acceptable arterial oxygen saturation remains debated but generally ranges between 85 and 92 %. Such an approach is seeing increased acceptance, despite the lack of definitive data, as this management strategy is based on physiologic principles (Cheifetz and Hamel 2006; Abdelsalam and Cheifetz 2010).

This clinical approach is based on the general relationship between oxygen saturation and partial pressure of oxygen in arterial blood (PaO_2). An oxygen saturation of 90 % generally correlates to an arterial blood gas PaO_2 of approximately 60 mmHg; however, depending on a range of clinical factors, variation in this relationship may occur due to shifts of the hemoglobin-oxygen dissociation curve (Fig. 43.3). Under normal circumstances, at a PaO_2 of 60 mmHg and an oxygen saturation of approximately 90 %, the hemoglobin-oxygen dissociation curve becomes flat due to its sigmoid shape, which means that

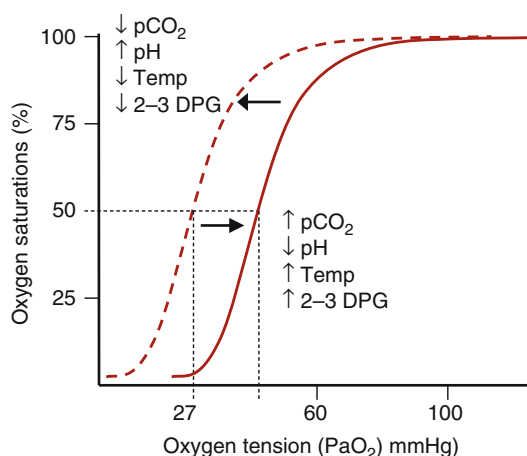


Fig. 43.3 Hemoglobin-Oxygen dissociation curve

increases in oxygen tension above 60 mmHg will only minimally impact oxygen content of the blood (CaO_2) and oxygen delivery (DO_2). Clinical assessments of global oxygen delivery must be closely assessed. Additionally, permissive hypoxemia must be used cautiously in those patients with significant anemia as arterial oxygen content can be greatly decreased.

The acceptability of permissive hypoxemia and permissive hypercapnia must be based on the specific clinical scenario and the pathophysiology involved. Each of these “permissive” strategies may allow the provider to avoid toxic ventilator settings, but these strategies are not uniformly applicable to all disease states. For example, it may not be reasonable to manage a patient with closed head injury with an elevated pCO_2 (causing increased cerebral blood flow) or a low oxygen saturation (potentially causing inadequate cerebral oxygen delivery). Likewise, a patient in shock or with significantly depressed myocardial function may not tolerate hypoxia (due to inadequate myocardial and global oxygen delivery).

These ventilatory targets represent a starting point for management, but there is clearly not a “one-size-fits-all” approach to mechanical ventilation. The pathophysiologic processes that lead to invasive mechanical ventilation in pediatrics are wide ranging, and the goals of mechanical ventilation should be largely driven by the combination of the underlying patho-

physiology. The aforementioned parameters should be adapted to more appropriately address an underlying disease in many circumstances. It is imperative that clinicians have a clear understanding of not only the underlying disease, but also the basic physiologic principles of mechanical ventilation and cardiorespiratory interactions.

Additionally, depending on the available technology, a number of other parameters may be important in the management of mechanically ventilated patients. End-tidal capnometry is an important indicator of the effectiveness of ventilation and carbon dioxide removal. Volumetric capnography expands on this principle and can assist providers in monitoring pulmonary blood flow, cardiac output, and anatomic and alveolar dead space. The dead space to tidal volume ratio (Vd/Vt) may provide important information regarding alveolar dead space and zone one ventilation. This fraction can be followed over time and may provide insight into the trajectory of disease progression. Vd/Vt has also been used as a predictor of extubation success (Newth et al. 2009; Hubble et al. 2000).

43.11 Influence of Maintaining Spontaneous Breathing During Mechanical Ventilation

Conclusive studies to demonstrate that any one mode of conventional mechanical ventilation is superior to another do not exist. However, most clinicians would agree that maintaining some degree of spontaneous ventilation regardless of the mode selected is important. The rationale for this approach is based on the notion that spontaneous ventilation improves patient comfort, secretion clearance, and neuromuscular strength. Also, minimizing sedation leads to a shorter duration of ventilation (Randolph et al. 2002).

Maintaining spontaneous breathing has been shown to decrease ventilation/perfusion mismatch and improve oxygenation (Varelmann et al. 2008). Spontaneous breathing decreases mean intrathoracic pressure, thus, allowing improved filling of the right atrium (i.e., preload to the

heart) and improved right ventricular output. More optimal cardiorespiratory interactions can be achieved during spontaneous respiration (Varelmann et al. 2008; Putensen et al. 2006).

Pressure support ventilation (PSV) can be utilized in conjunction with other modes of ventilation or independently to maintain spontaneous breathing during mechanical ventilation. PSV has been demonstrated in adults to decrease patient work of breathing, and this modality is more frequently being utilized in pediatric respiratory failure (Banner et al. 1991). There are a number of potential physiologic benefits to this approach to spontaneous ventilation as it allows patients to regulate respiratory rate, inspiratory flow, and inspiratory time.

In addition to PSV, the current generation of ventilators offers nontraditional modes of ventilation, which aim to facilitate both spontaneous breathing and patient-ventilator synchrony. As previously described in this chapter, these approaches include proportional assist ventilation (PAV), neurally adjusted ventilatory assist (NAVA), and adaptive support ventilation (ASV) (Beck et al. 2007; Colombo et al. 2008; Schmidt et al. 2010; Spahija et al. 2010; Terzi et al. 2010; Sinderby et al. 2007; Barwing et al. 2009; Coisel et al. 2010; Alander et al. 2012; Bengtsson and Edberg 2010; Younes 1992; Kacmarek 2011; Giannouli 1999; Kondili et al. 2006; Wrigge et al. 1999; Xirouchaki et al. 2008).

Allowing a patient to determine their own respiratory rate will generally result in more normal arterial blood gases. When spontaneous breathing is maintained, respiratory rate may then be followed as a marker for the trajectory of lung disease. One specific situation in which the maintenance of spontaneous respiratory effort may be beneficial is bronchospasm/prolonged exhalation. Air trapping may be worsened by an insufficient expiratory time in these situations, and a patient's native respiratory rate will often better achieve ventilatory goals than one set by the bedside provider.

In the pediatric patient, minimizing pharmacologic sedation to promote spontaneous breathing can be challenging, as fear and anxiety in children occur more commonly than in adults. Optimizing patient-ventilator synchrony with

decelerating flow, adequate pressure support, appropriate inspiratory time, and appropriate flow triggers should minimize sedation requirements and, in turn, lead to a shorter duration of ventilation (Cheifetz 2003; Newth et al. 2009; Randolph et al. 2002).

The implications of spontaneous breathing on ventilator weaning have been extensively investigated, but results remain inconclusive regarding the benefit of this approach in pediatrics. Spontaneous breathing trials are standard in the adult patient population, but within pediatrics, no specific technique for ventilator weaning has been demonstrated to be superior (Randolph et al. 2002). Further clinical investigation is warranted to determine the impact of spontaneous breathing on overall outcomes in the management of pediatric acute respiratory failure.

43.12 Special Populations

43.12.1 Small Airways Disease

Patients with small airway disease require interventions directed at reversing bronchospasm, increasing alveolar ventilation, and promoting the exchange of retained alveolar gas with inspired gas. In this context, the initial approach should be to increase the expiratory time by reducing the respiratory frequency on the ventilator, while maintaining an appropriate inspiratory time. As the respiratory frequency is reduced, tidal volume may need to be increased to maintain minute ventilation and provide adequate alveolar ventilation. If this intervention does not allow for adequate alveolar emptying, further reduction of inspiratory time to lower levels may be employed as long as adequate time remains for inspired gas to be delivered to the alveoli without elevating peak airway pressures.

43.12.2 Postoperative Cardiac Patients

Invasive mechanical ventilation can have a substantial impact on both the lungs and heart as well as the complex interactions between these

thoracic organs. Cardiopulmonary interactions are an important consideration as invasive mechanical ventilation is initiated, and clinicians must carefully determine the effects of ventilatory maneuvers on cardiac output, especially in the postoperative congenital heart patient. This monitoring can largely be done noninvasively via echocardiography, capnography, and cerebral oximetry. Additional invasive monitoring and evaluation may include laboratory measurements of blood gases, lactic acid, and mixed venous saturations. Ventilatory management implications in specific cardiac situations are described in further detail below. (See also Chap. 53.)

43.12.2.1 Right Ventricular Dysfunction

Patients with right ventricular (RV) dysfunction, a common problem in the immediate postoperative period for the congenital cardiac surgical patient, will benefit from manipulations of cardiorespiratory interactions to optimize RV preload and minimize RV afterload. Since the majority of pulmonary blood flow occurs during expiration, inspiratory time in these patients should be short compared to expiratory time to enhance right-sided cardiac output. In addition, patients with RV dysfunction are particularly sensitive to changes in intrathoracic pressure since cardiac output is preload dependent. These patients may benefit from ventilation strategies which lead to a reduction in the mean intrathoracic pressure.

This approach may involve reducing the positive end-expiratory pressure and/or inspiratory time. However, the clinician should be cautioned that reducing mean airway pressure to the point of lung collapse will increase pulmonary vascular resistance (i.e., increase right ventricular afterload). This complex balance must be carefully assessed for each individual patient over time.

As lung disease worsens, high-frequency jet ventilation (HFJV) may be considered in patients with RV dysfunction who require mean airway pressures >10–15 cm H₂O. HFJV often allows for a reduction of mean airway pressure, improved RV preload, and increased RV cardiac

output as compared to conventional ventilation (Meliones et al. 1991).

In addition, the RV response to ventilatory manipulations is exacerbated in patients with concomitant hypovolemia due to the preexisting reduction in RV preload. Therefore, strict attention to intravascular volume status is required in patients with RV dysfunction and elevated mean intrathoracic pressures. While this approach to optimizing RV preload and afterload through manipulation of cardiopulmonary interactions is well accepted and based on sound physiologic principles, limited outcome data exist to guide practitioners in the detailed implementation of this strategy.

43.12.2.2 Left Ventricular Dysfunction

In patients with left ventricular (LV) dysfunction, especially in the postoperative period, cardiorespiratory interactions should be directed at optimizing LV function (Meliones et al. 1991; Deal et al. 1970; Jenkins et al. 1985; Nelson 1966). The ventilatory strategy for patients with LV dysfunction often consists of increasing the mean airway pressure to decrease LV afterload and improve global cardiac output. The effects of mechanical ventilation on LV preload are more variable and often dependent on the RV effects of the increased mean intrathoracic pressure (i.e., ventricular interdependence) as described above and elsewhere in this textbook (Chap. 53).

Conclusions

New ventilators with improved pediatric interfaces along with continued advancements in lung-protective ventilatory strategies promise to improve outcomes for mechanically ventilated children. A wide range of issues must be carefully considered as mechanical ventilator parameters are established. These considerations not only include the settings themselves, but also the patient's underlying disease process, age, size, pathophysiologic state, and the potential implications of invasive ventilation on other organ function. Furthermore, there is an increasing quantity of research evaluating ventilator management in

infants and children, including a focus on the interaction between mechanical ventilation and the management of other organ systems. The summation of new technologies and a growing base of evidence will allow providers to continue to optimize the mechanical ventilator management and respiratory care for critically ill infants and children.

Essentials to Remember

- No single ventilator strategy can be applied to all patients due to substantial variation in disease processes.
- Optimal ventilatory management should be directed at lung protection to prevent VILI. Unfortunately, specific pediatric data are lacking to definitively guide management.
- No conclusive data exist to support the superiority of any one mode of conventional mechanical ventilation over another.
- Ventilator targets for infants and children with acute lung injury are primarily extrapolated from adult studies, including maintaining tidal volume on 6 ml/kg ideal body weight, avoiding peak inspiratory pressures greater than 30 cm H₂O, and maintaining FiO₂ less than approximately 0.50.
- Permissive hypercapnia and permissive hypoxia should be considered to optimize lung protection for those with severe ARDS. However, it should be noted that definitive data are lacking.
- Spontaneous breathing is an important component of most mechanical ventilation strategies, and promotion of spontaneous breathing may lead to a decreased length of ventilation.
- Ventilator targets must be adapted based on an individual patient's underlying disease process, age, size, and pathophysiologic state along with the potential implications of ventilation strategies on pulmonary and nonpulmonary organ function.

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Ira M. Cheifetz and David A. Turner

Educational Aims

- Understand the use of ventilator graphics in the assessment of patient-ventilator synchrony.
- Review the impact of specific acid-base disturbances on patient-ventilator synchrony.
- Understand the difference between flow and trigger dys-synchrony and the corresponding treatments.
- Recognize the importance of ventilator graphics in the titration of positive end-expiratory pressure (PEEP).
- Review the physiology of airway obstruction as it relates to airway graphics and patient-ventilator synchrony.
- Review the importance of ventilator graphics in the setting of airway obstruction, acute lung injury, hemodynamic instability, and cardiac disease.

44.1 Assessing Patient-Ventilator Interactions

Most mechanical ventilators in neonatal and pediatric intensive care units provide continuous monitoring of respiratory variables as well as a graphical display of gas flow, tidal volume, and airway pressure. Routine analysis of these waveforms is an important aspect of the assessment of patient-ventilator interactions and should be used to optimize mechanical ventilatory support. The ventilator can be titrated using airway graphics and waveforms to improve patient-ventilator synchrony, reduce patient work of breathing, and calculate physiologic parameters related to respiratory mechanics.

Volume delivery is generally determined by integrating the inspiratory flow signal over time, and airway graphics are most commonly displayed as scalars (flow, pressure, and volume graphed over time) (Fig. 44.1) and loops (pressure volume and flow volume) (Fig. 44.2). For airway scalars, the horizontal axis depicts time, and the vertical axis displays the measured variable (flow, pressure, or volume), and these airway scalars are an important component of the assessment of patient-ventilator synchrony. It should be noted that synchrony should be assessed for both the inspiratory and expiratory phases of respiration.

In contrast to scalars, airway loops depict one variable in relation to another, rather than versus time (Fig. 44.2). The airway loops are particularly helpful in assessing alterations in airway

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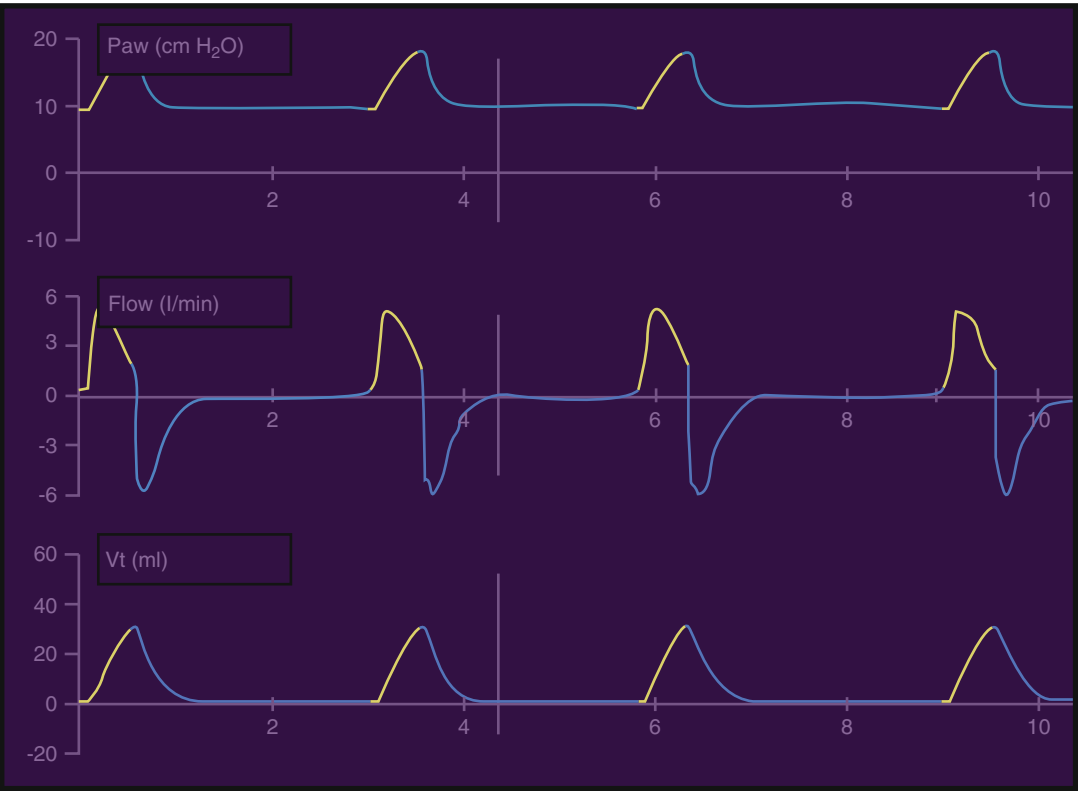


Fig. 44.1 Airway scalars. Airway pressure (Paw), flow, and volume (Vt) are graphically displayed over time

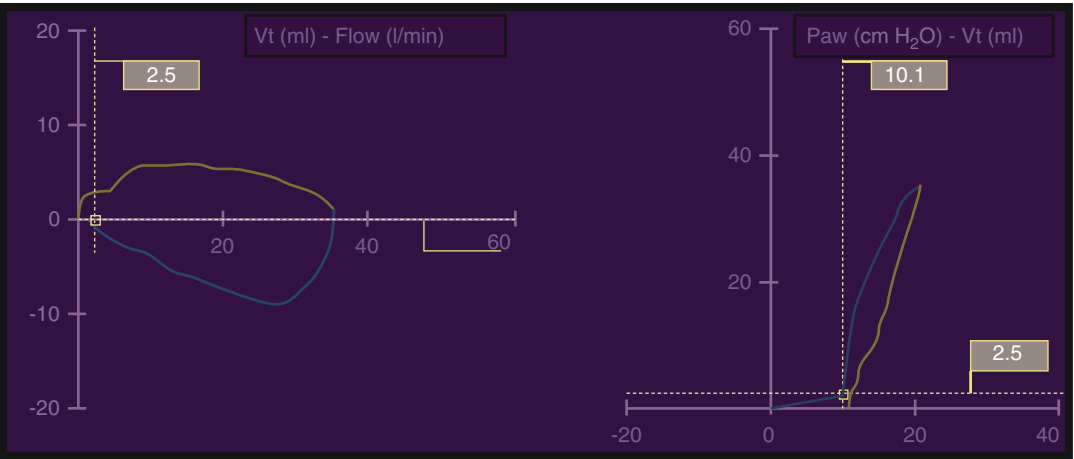


Fig. 44.2 Airway loops. Flow-volume (Vt) and pressure (Paw)-volume (Vt) loops as typically displayed by most ventilators with inspiration being represented by the yellow lines and expiration represented by the blue lines

resistance, pulmonary compliance, patient work of breathing, pulmonary overdistension, and “gas trapping” (i.e., premature termination of

exhalation). The standard pressure-volume loop graphs pressure on the horizontal axis and volume on the vertical axis. On the pressure-volume

curve, the slope of the inspiratory limb represents compliance. Flow-volume loops depict flow on the vertical axis and volume on the horizontal axis. These loops also can be employed to assess a number of important aspects of ventilator management, including large and small airway obstruction as well as expiratory airway resistance.

The overall goal of this section is to provide clinicians with an approach to optimizing mechanical ventilation strategies using a comprehensive, but simple, bedside assessment of patient-ventilator interactions through the analysis of airway graphics.

**44.2 Respiratory Alkalosis/
Acidosis: Alveolar Ventilation**

**44.2.1 Increased Ventilatory
Requirements**

The elimination of the carbon dioxide (CO₂) produced from the metabolic processes throughout the organs and tissues of the body is a vital function of the respiratory system. Inadequate alveolar ventilation and CO₂ clearance secondary to respiratory muscle failure is one of the most common reasons for inability to wean from mechanical ventilation in the neonatal and pediatric populations.

Respiratory pump failure may be due to decreased ventilatory capacity and/or increased respiratory muscle load; either of which may, in turn, be secondary to a wide range of disturbances including shock, hypoxemia, and hypercapnia (Table 44.1). Diminished effective tidal volume delivery created by impaired respiratory muscle function leads to inadequate alveolar ventilation and, subsequently, respiratory acidosis. Clinically, this respiratory muscle dysfunction is often demonstrated as the development of tachypnea. In this context, the presence of hypercapnia despite a significant increase in respiratory rate should be concerning and generally represents an indication to discontinue weaning from mechanical ventilatory support.

Table 44.1 Typical causes of respiratory pump failure

<i>Decreased ventilatory capacity</i>
Respiratory muscles
Hyperinflation
Malnutrition
Metabolic derangements
Decreased oxygen supply
Disuse atrophy
Fatigue
Abdominal wall defects
Neurologic
Decreased respiratory center output
Cervical spinal cord surgery
Phrenic nerve dysfunction
<i>Increased respiratory muscle load</i>
Increased ventilatory requirements
Increased CO ₂ production
Increased dead space ventilation
Inappropriately elevated ventilatory drive
Increased work of breathing
Decreased efficiency of breathing
Increased chest wall compliance
Respiratory pattern

Failure to wean from mechanical ventilation may also result from increased ventilatory requirements, which can be secondary to increased CO₂ production. Reasons for increased CO₂ production include excessive carbohydrate intake, fever (10 % increase for each °C), and excessive muscle activity (e.g., seizing, shivering, rigors). In this setting, augmenting alveolar ventilation may be necessary to maintain normocarbica. Another reason that increased minute ventilation may be necessary to maintain effective ventilation is to compensate for an increased ratio of physiologic dead space to tidal volume (V_D/V_T) as occurs with decreasing pulmonary capillary blood flow (which is often caused by a low cardiac output state), significant obstruction of the airways, or excessive distending airway pressures. Finally, excessive respiratory drive from psychological stress, central nervous system abnormalities, or pulmonary receptor stimulation may stimulate inappropriate hyperventilation and a secondary increase in respiratory muscle load.

44.2.2 Respiratory Acidosis

Hypercapnia and associated respiratory acidosis are the consequence of inadequate CO₂ elimination in relation to production and may develop during the weaning phase of mechanical ventilation. This respiratory acidosis can have clinically significant effects including alterations on pulmonary vascular resistance (PVR), ventricular performance, systemic hypertension, ventricular ectopy, and catecholamine release. Hypercapnia may be caused by inadequate CO₂ elimination, increased production, and/or an airway obstructive process.

Airway obstruction results in an inadequate CO₂ elimination when inspired gas is unable to reach the alveoli or, more commonly, when alveolar gas is unable to be exhaled. Obstructive airways disease may be inspiratory and/or expiratory and can be caused by pathology of the alveoli, small airways, and/or larger airways. Irrespective of the location of the obstruction, the end result of inadequate effective alveolar ventilation is manifested by a decrease in effective V_T , leading to tachypnea and possibly hypercapnea.

Hypercapnia, in and of itself, does not necessitate intervention and in many circumstances is not harmful (Peltekova et al. 2010; Laffey et al. 2000; Ni Chonghaile et al. 2005; Kavanagh et al. 2006). There is evidence to support permissive hypercapnia as a ventilatory strategy in which the partial pressure of arterial carbon dioxide (PCO₂) is allowed to increase as long as an “acceptable” pH is maintained. Of course, “acceptable” values for pH and PaCO₂ vary between individual patients, within an individual patient over time, and among clinicians.

However, the respiratory acidosis associated with significant hypercapnia can have detrimental effects on ventricular function and the pulmonary vasculature. When respiratory acidosis develops, an appropriate increase in the delivered tidal volume may be required to increase minute ventilation and correct the associated hypercapnia. While there are various noninvasive techniques (i.e., capnography and transcutaneous monitoring) to assess CO₂ elimination, arterial blood gas analysis is most commonly utilized. As PaCO₂ is inversely related to alveolar ventilation, a reduction in minute ventilation by 50 % results

in a doubling in the PaCO₂. As ventilator interventions are implemented to improve acidosis and reduce PaCO₂, airway pressure and delivered tidal volume should be monitored to ensure that they remain within the nontoxic range as ventilatory support is increased.

In the assessment of unexplained hypercapnea and respiratory acidosis, patient-ventilator dys-synchrony is an important consideration. This abnormality in the relationship between the patient and the ventilator may cause an individual to compensate for the abnormal patient-ventilator interactions by increasing spontaneous respiratory effort, which may further exacerbate the patient-ventilator dys-synchrony. Patient-ventilator dys-synchrony most commonly occurs if overall ventilatory support is inadequate, the inspiratory flow does not meet patient demand, and/or the trigger is not adequately sensitive. Patient agitation related to dys-synchrony may undermine ventilatory interventions, require ventilator adjustments, generally in the flow and/or trigger settings, and necessitate an increase in sedation and/or neuromuscular blockade to improve gas exchange, as discussed later in this chapter (Epstein 1971; Gibney et al. 1982; Greenough et al. 1983; Stark et al. 1979).

44.2.3 Respiratory Alkalosis

Respiratory alkalosis is generally less common (and less clinically concerning) in the intensive care unit setting than respiratory acidosis. Compensatory respiratory alkalosis develops in most spontaneously breathing patients as a response to significant metabolic acidosis. Treatment of the underlying metabolic process is essential along with (or prior to) ventilator interventions to correct a respiratory alkalosis. It should be noted that in a mechanically ventilated patient with a primary metabolic acidosis, ventilator weaning could have a profound impact on pH, exacerbating the overall acidotic state.

Another cause of respiratory alkalosis is neurologic dysfunction and an inappropriate stimulation of the central nervous system. An abnormal respiratory drive will induce respiratory alkalosis secondary to intrinsic abnormalities of the

respiratory centers of the brain. In this situation, the underlying process should be fully assessed and addressed as clinically indicated.

44.3 Patient-Ventilator Dys-synchrony

Patient-ventilator dys-synchrony occurs when a patient's spontaneous inspiratory effort is out of phase with the positive pressure breaths of the ventilator, resulting in a patient "fighting" the ventilator. When ventilatory support is dys-synchronous with patient effort, oxygen (O_2) consumption of the respiratory muscles may be excessively high and creates an imbalance between O_2 delivery and consumption. This additional respiratory effort and dys-synchrony may lead to a reduction in the effective tidal volume delivery and a subsequent respiratory acidosis. Patient-ventilator dys-synchrony is diagnosed by careful observation of the patient and a comprehensive assessment of the ventilator's airway graphical display. In the differential, ventilation/perfusion mismatch, mucous plugging, pneumothorax, and reactive airways disease must be considered. Once these causes are addressed, altering ventilatory mode, increasing overall ventilator support, adjusting inspiratory flow, improving trigger sensitivity, and/or administering pharmacologic sedation (preferably as a last intervention) will generally improve synchrony between the patient and the ventilator.

44.3.1 Patient-Ventilator Interactions

Graphical waveforms are useful in the assessment of the characteristics of ventilator function and provide a graphical display of the impact of mechanical ventilatory strategies. The timing sequence of various ventilatory events relative to a patient's respiratory effort can be assessed by airway scalars (Fig. 44.1). Ventilator dys-synchrony becomes evident when the timing and magnitude of pressure, volume, and especially flow are disproportionate or delayed. Using airway graphics analysis, clinicians can titrate ventilator breaths to improve patient-ventilator synchrony, reduce

patient work of breathing, and calculate a variety of physiologic parameters related to respiratory mechanics (Tobin et al. 2001).

Airway graphic analysis can be used to continually assess respiratory pathophysiology by evaluating inspiratory flow, tidal volume, airway pressures, compliance, airways resistance, and pressure-volume and flow-volume relationships. Airway graphic analysis can assist with determining the effectiveness of respiratory interventions and changes in a patient's respiratory status over time. In addition to patient-ventilator dys-synchrony (including excessive patient work of breathing), abnormalities frequently diagnosed by airway graphic analysis include pulmonary overdistension, excessive air leak, premature termination of exhalation/dynamic hyperexpansion ("gas trapping"/intrinsic positive end-expiratory pressure (PEEPi), inspiratory and expiratory airway obstruction, and increased airways resistance.

44.3.2 Trigger Dys-synchrony

Trigger insensitivity/dys-synchrony is the inaccurate sensing of a patient's inspiratory effort, which can result in either the failure of a ventilator to respond to a patient's effort or the auto-triggering of a ventilator without any patient effort. An intubated patient's attempt to inspire results in a decrease in the airway flow and/or pressure from baseline in the ventilator circuit, which should trigger a ventilator-assisted or ventilator-supported breath. However, when trigger sensitivity is inadequate, the ventilator may be unable to determine that patient effort has actually occurred, as seen in by the first three breaths in Fig. 44.3. Equally problematic, as seen in breath 4 in Fig. 44.3, the ventilator may deliver a full mechanical breath without regard to patient effort. When a patient's effort is inadequately sensed, this trigger dys-synchrony can result in tachypnea, increased work of breathing, and patient discomfort ("fighting the ventilator").

Adjustments in the sensitivity of the trigger can substantially improve patient-ventilator synchrony when patient effort is not appropriately being sensed by the ventilator. Flow triggering is

Fig. 44.3 Trigger dys-synchrony. Deflection in the flow tracing without an appropriate deflection in the pressure tracing reflects a breath not sensed by the ventilator (*red arrows*). Although the patient can move a flow of gas by breathing the bias flow available in the circuit, the patient effort is inadequate to generate a full mechanical or pressure support breath. The *black arrow* denotes a ventilator breath being initiated during patient exhalation secondary to inadequate trigger sensitivity

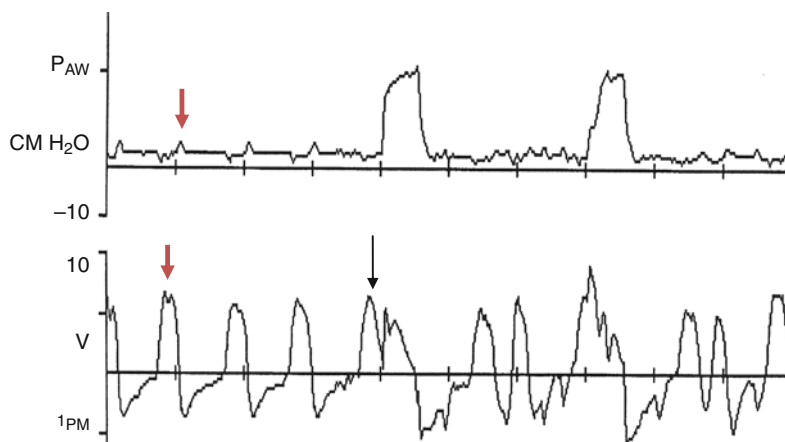
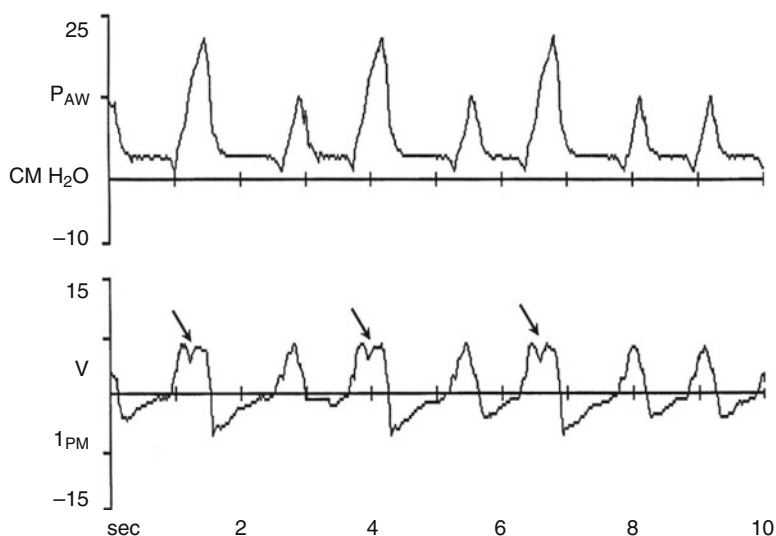


Fig. 44.4 Inspiratory flow dys-synchrony as demonstrated by the flow-time airway scalar. *Arrows* represent patient effort in the setting of inadequate flow



generally more sensitive than pressure triggering as a change in flow requires less inspiratory effort than a pressure change. Thus, flow triggering is used most commonly in neonatal and pediatric critical care as a mechanism to improve patient-ventilator synchrony and minimize issues with trigger sensitivity.

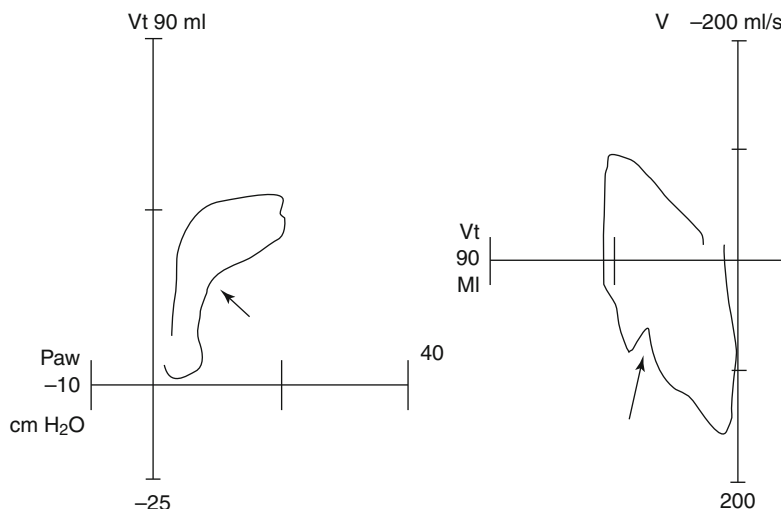
Dys-synchrony may also occur when an excessive air leak initiates unwarranted ventilator triggering. In this situation, the ventilator may not be able to distinguish the difference between a decrease in airway flow/pressure due to the excessive air leak and inspiratory effort by the patient. Thus, a large air leak may be misinterpreted by a ventilator as patient effort, resulting in “autocycling” of an inappropriately triggered

ventilator breath (i.e., without patient effort). In such situations, the trigger sensitivity setting should be adjusted and/or the air leak addressed.

44.3.3 Flow Dys-synchrony

In addition to trigger insensitivity, inadequate inspiratory flow can lead to patient-ventilator dys-synchrony. Figure 44.4 reveals a patient effort which results in a decrease in airway pressure (arrows); however, as inspiratory flow is limited in this square-wave, constant flow mode of ventilation, the ventilator is unable to deliver the inspiratory flow the patient desires. In this situation, patient effort creates a transient reduction of

Fig. 44.5 Inspiratory flow dys-synchrony as demonstrated by a flow-volume loop. *Arrows represent patient effort secondary to inadequate flow*



airway pressure during inspiration, and flow dys-synchrony is demonstrated by a decrease in the airway pressure tracing on the pressure-time scalar. The clinical findings of this “double breath” are typically tachypnea and increased work of breathing, along with overall patient discomfort and agitation. This dys-synchrony may also be similarly seen on the flow-volume loop as indicated by the arrow (Fig. 44.5).

Increasing the set inspiratory flow rate during square-wave, constant flow ventilation and/or increasing the overall ventilatory support may eliminate flow dys-synchrony; however, such an approach may lead to an unacceptable increase in the peak inspiratory pressure (PIP). In such a situation, changing to an alternate mode of ventilation with variable inspiratory flow may be helpful in improving synchrony. A variable, decelerating inspiratory flow mode will generally meet the inspiratory demand better than a mode with constant inspiratory flow (e.g., volume-limited ventilation).

Although flow dys-synchrony is most commonly seen in constant, square-wave inspiratory flow ventilation (e.g., volume-limited ventilation) as previously described, flow dys-synchrony can occur with decelerating, variable inspiratory flow ventilation when the patient is at the upper limits of the settings chosen (i.e., neonatal or pediatric settings of the ventilator). For example, a large infant with a strong inspiratory demand may demonstrate flow dys-synchrony when the infant

ventilator settings are utilized. In this situation, the flow dys-synchrony can be resolved by changing to a pediatric circuit and adapting ventilator settings to increase maximal inspiratory flow.

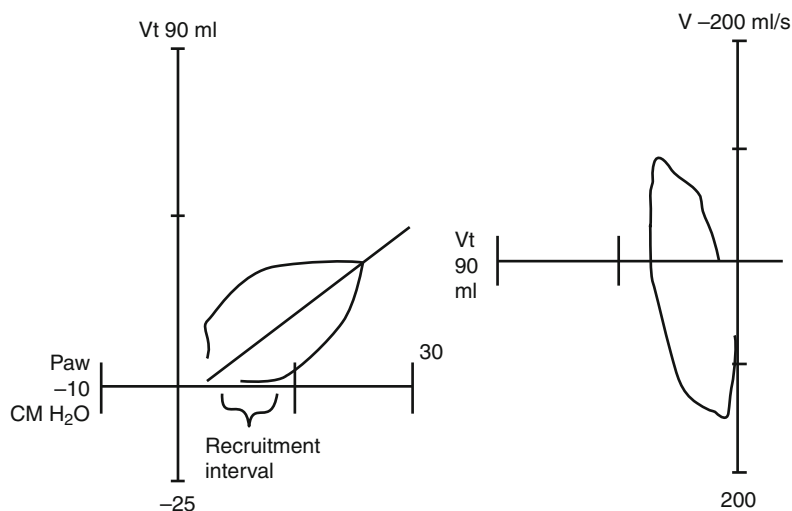
44.4 Optimizing PEEP

44.4.1 Acute Lung Injury

Acute lung injury (ALI) results in the loss of alveolar stability, alveolar collapse, and decreased pulmonary compliance (Kavanagh et al. 2006; Caironi et al. 2010; Gattinoni et al. 2006; Martin et al. 1992) as seen by a decrease in the slope of the pressure-volume loop (Fig. 44.6). Alveolar collapse may reduce functional residual capacity (FRC) during expiration, if the airway pressures are not adequate to maintain patency of the alveoli at end expiration. In Fig. 44.6, PEEP is inadequate to maintain alveolar patency at end expiration and results in significant atelectasis. During the initial portion of inspiration, re-expansion of collapsed alveoli must occur, and due to the decreased pulmonary compliance, airway pressure must be substantially increased before gas delivery to the alveoli occurs.

The cost of re-expansion of a de-recruited lung is the amount of airway pressure needed to achieve an opening volume (recruitment interval). To deliver a given volume of gas, the presence of alveolar collapse increases the required

Fig. 44.6 Decreased pulmonary compliance associated with acute lung injury as demonstrated by a flattening of the pressure-volume curve



pressure for re-expansion, thus, elevating both the opening pressure and the peak inspiratory pressure. In essence, tidal volume can only be delivered after this critical opening volume is reached, and the pressure required to achieve the opening volume increases as compliance falls.

Optimizing PEEP is an essential management strategy for acute lung injury to minimize the repetitive opening and closing of alveolar units and its associated atelectrauma (Borges et al. 2006; Brower et al. 2004; Meade et al. 2008; Mercat et al. 2008). Increasing the set PEEP will increase FRC with a larger quantity of alveoli patent at end expiration. As lung is recruited and appropriate PEEP is set, a lower PIP will be required to deliver a given tidal volume for the same inspiratory time. Optimizing PEEP generally improves pulmonary compliance with a decrease in PIP during volume-limited ventilation (or a higher Vt for a set PIP during pressure-limited ventilation). These effects may become more remarkable over time as the increased PEEP continues to recruit collapsed alveoli.

However, it must be noted that excessive PEEP can adversely affect cardiorespiratory function, including an (1) impedance to systemic venous return and an associated decrease in cardiac output secondary to the increased intrathoracic pressure (ITP) and/or (2) overdistension of relatively healthy lung alveoli with a redistribution of blood flow to more diseased alveoli (i.e., ventilation/perfusion mismatch). To optimize

PEEP using airway graphics, PEEP should be titrated until the best balance is achieved: lowest PIP to deliver the desired Vt, highest compliance, and optimum O₂ delivery (requires a determination/estimation of cardiac output).

There are two general strategies for optimizing PEEP. One involves a gradual increase in PEEP while assessing cardiorespiratory parameters (i.e., incremental PEEP). The second option involves a significant and rapid increase in the mean airway pressure and then a gradual reduction until the “optimal PEEP” is obtained (i.e., decremental PEEP). There are no conclusive data demonstrating that either approach is more optimal.

Numerous physiologic attempts have been made to determine “optimal PEEP” by total O₂ delivery. The level of PEEP associated with maximal O₂ delivery may coincide with maximal respiratory compliance (Suter et al. 1975). However, defining optimal PEEP in this manner has been criticized as decreased O₂ delivery may occur secondary to a decrease in cardiac output as associated with the elevated mean ITP and a resultant decreased systemic venous return. This adverse cardiorespiratory interaction can be generally reversed by supplementing intravascular volume (i.e., right ventricular preload) and/or initiating inotropic support (i.e., ventricular contractility). Such an approach allows for a higher PEEP to be administered while maintaining cardiac output (i.e., right ventricular output) and,

hopefully, optimizing global O_2 delivery (Suter et al. 1975; Hemmer and Suter 1979; Qvist et al. 1975; Venus et al. 1979). Continuous evaluation of the cardiorespiratory effects of ventilator manipulations are essential, and if refractory hypoxia persists despite further escalation of the mean airway pressure, high-frequency ventilation or extracorporeal life support may be considered.

44.4.2 Ventilation-Perfusion Mismatch

In the setting of acute lung injury, ventilation/perfusion mismatch often leads to hypoxemia. This is especially true for the infant population due to differences in lung physiology, which includes a reduced FRC, an increased closing capacity, and increased airway collapse during normal tidal breathing (Garson and Gillette 1979; Gewillig et al. 1990; Gillette et al. 1980; Hickey and Hansen 1984). As previously noted, pressure-volume relationships and airway graphics can be used to assess changes in lung volume, compliance, and FRC. Ventilation-perfusion mismatch may also create significant intrapulmonary shunting, which may be confirmed by the calculation of the alveolar-to-arterial oxygen gradient (A-a gradient). Clinically, when a patient breathes FiO_2 1.0, a resultant PaO_2 of less than 500 mmHg in the absence of intracardiac shunting indicates a clinically significant intrapulmonary shunt.

Treatment for arterial hypoxemia as caused by ventilation-perfusion mismatch involves optimization of the ventilator settings and, most importantly, an establishment of appropriate PEEP, as described above. If hypoxemia remains refractory to an investigation for a treatable etiology and an escalation of ventilatory support continues, alternative modes of ventilation (i.e., high-frequency ventilation) and/or extracorporeal support may be indicated.

44.5 Airway Obstruction

Small or large airway obstruction may compromise ventilation; however, clinical findings will vary depending on the level of obstruction. Careful clinical examination and assessment of

airway graphics can help localize the level of the obstruction and, thus, assist in guiding appropriate therapeutic interventions. Airway obstruction may involve inspiration, expiration, or both. Expiratory airway obstruction is generally associated with decreased chest excursion and expiratory wheezing. As obstruction progresses and expiratory airflow continues to decrease, nearly absent breath sounds may become evident. In contrast, patients with a mechanical obstruction (e.g., foreign body aspiration) will generally demonstrate asymmetric breath sounds, and in patients with upper airway obstruction, inspiratory stridor will be noted on auscultation.

With mechanical obstruction of the larger airways, areas of hypo-aeration will likely be seen adjacent to areas of normal lung. In severe cases, lobes or an entire lung may collapse. In contrast, the pathophysiology of small airway obstruction caused by bronchospasm differs from that seen with large airways. Bronchospasm creates small airway obstruction impeding alveolar gas from being adequately exhaled (i.e., gas trapping), thus, resulting in the development of intrinsic PEEP, increased lung volume, and increased dead space ventilation. In this context, chest radiography demonstrates hyperlucent lung and overall increased lung volumes. Respiratory mechanics are diagnostic of lower airway obstruction and will show an increase in expiratory resistance and gas trapping as described in more detail below.

44.5.1 Flow-Volume Loops Demonstrating Airway Obstruction

Flow-volume loops demonstrate inspiratory and expiratory flow patterns. Abnormalities may be seen with kinked or blocked endotracheal tubes, bronchospasm, and anatomic or mechanical airway obstruction. The presence of airway obstruction and response to various interventions can be assessed by analysis of flow-volume loops. In Fig. 44.7, inspiratory flow is represented above the baseline as a decelerating wave with expiratory flow below baseline. During exhalation, failure of expiratory flow to return to baseline, representative of severe expiratory airway obstruction, is

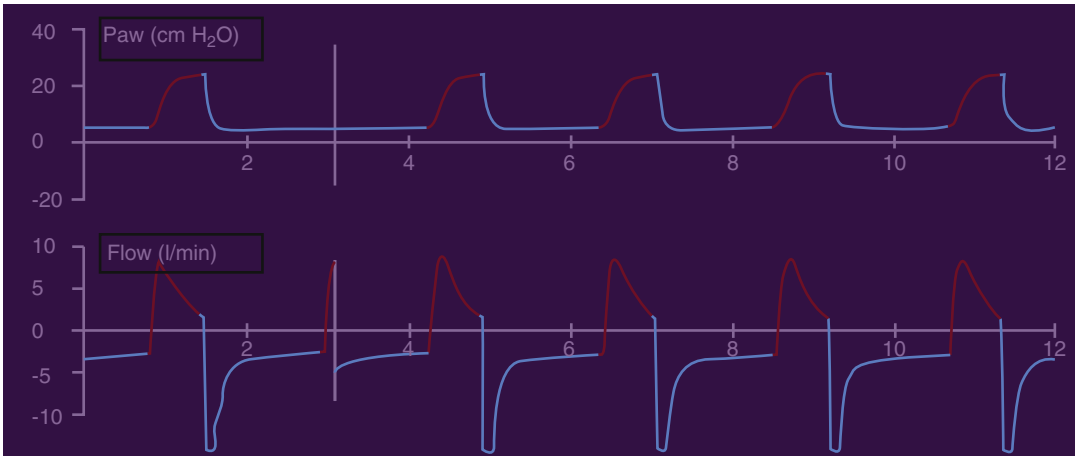


Fig. 44.7 Expiratory airway obstruction as seen in a flow-time scalar. Note the expiratory limb (blue lines) of the flow-time scalar does not return to baseline secondary to incomplete exhalation

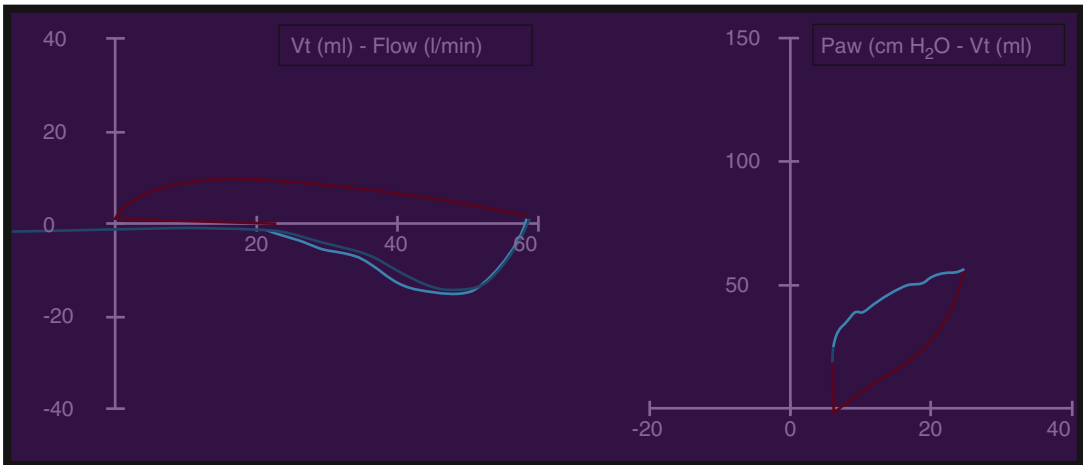


Fig. 44.8 Expiratory airway obstruction as seen on flow-volume loop

seen. In Fig. 44.8, the same expiratory airway obstruction is demonstrated on the flow-volume loop as expiratory flow (below the horizontal) does not return to the pre-inspiratory point.

44.6 Dynamic Hyperinflation

44.6.1 Detection of Overdistension Using Pressure-Volume Loops

Pulmonary overdistension is defined as an abrupt decrease in compliance at the termination of a breath (Fig. 44.9). Overdistension occurs when the volume limit of the lung is approached and a

subsequent increase in the delivered airway pressure is associated with a relatively smaller volume change. This situation results in a decrease in pulmonary compliance, which is reflected by a reduction in slope of the inspiratory loop (i.e., upper inflection point) and terminal “beaking” of the pressure-volume curve. Pulmonary overdistension is defined as the compliance of the last 20 % of inspiration being less than the compliance of the total breath ($C_{20}/C_{total} < 1.0$). Such a change in compliance due to overdistension may result in volutrauma and potentially an elevation of pulmonary vascular resistance as overdistended alveoli compress their surrounding capillaries. To prevent this occurrence, an excessive

set PIP/delivered tidal volume should be avoided, and pressure-volume loops should be monitored on a regular basis. Additionally, it should be noted that excessive PEEP may lead to overdistension of the more compliant lung regions.

44.6.2 Dynamic Hyperinflation and Intrinsic PEEP

Premature termination of exhalation results in dynamic hyperexpansion and “gas trapping.” This is seen in Fig. 44.10, where there is inadequate time for complete exhalation. In

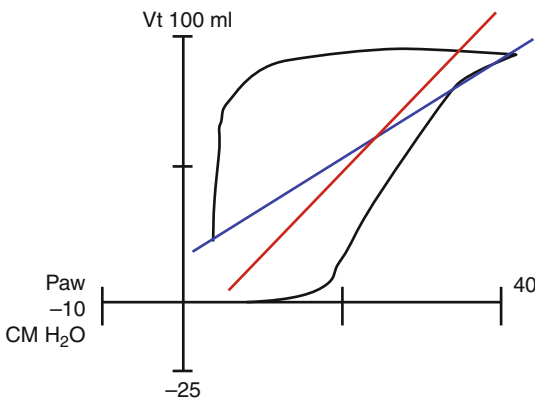


Fig. 44.9 Pressure-volume loop demonstrating pulmonary overdistension in which the compliance of the last 20 % of inspiration (blue line) is less than the total compliance (red line) for the breath

most situations, “gas trapping” and dynamic hyperexpansion/hyperinflation are synonymous terms. Gas trapping may result in intrinsic PEEP (PEEPi), which elevates the baseline airway pressure (set PEEP + PEEPi). Such an increase in the baseline airway pressure results in an increased total delivered PIP in ventilatory modes in which tidal volume or delta-P is set and a decreased delivered tidal volume when peak inspiratory pressure is limited.

Adverse effects of intrinsic PEEP include an increase in mean airway pressure due to the inadvertent increase in end-expiratory pressure. Such an increase in mean ITP may adversely affect cardiac output as previously described. Additionally, patients who are spontaneously breathing need to overcome this additional pressure to trigger a ventilator, if the ventilator is set to pressure trigger. PEEPi may increase patient work of breathing and contribute to muscle fatigue. One solution is to transition to flow triggering.

It should be noted that intrinsic PEEP, theoretically, may be desirable in the management of ARDS as it may improve oxygenation due to the elevated mean airway pressure. However, intrinsic PEEP is relatively uncontrolled as compared to set PEEP, and set PEEP can be more reliably titrated to achieve the desired oxygenation. Careful monitoring for intrinsic PEEP is required to limit the development of secondary lung injury and hemodynamic compromise due to the associated increase in mean ITP. PEEPi can generally

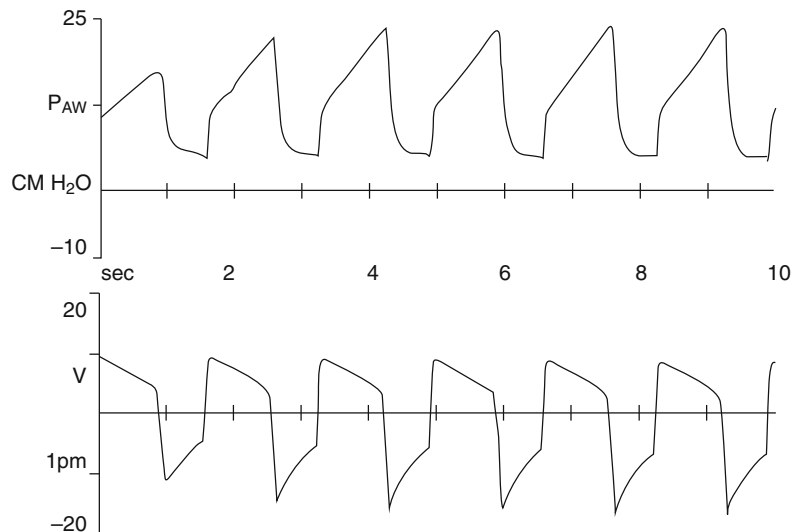


Fig. 44.10 Premature termination of exhalation and intrinsic PEEP. Note the expiratory flow does not return to zero (baseline) secondary to “gas trapping” or inadequate exhalation

be determined using an end-expiratory hold maneuver on the ventilator. Some monitors/ventilators determine PEEP_i by assessing the difference between the set PEEP and the airway pressure immediately prior to the initiation of inspiration.

44.6.3 Airway Graphics: Summary

With technical advances in providing mechanical ventilation, clinicians have multiple ventilatory modes and numerous parameters to set and monitor. Airway graphics analysis provides invaluable tools to assist in determining an individualized approach for each patient based on pathophysiology as well as to assess the efficacy of the management strategy. Airway graphics provide a rapid assessment of ventilatory parameters in “real time,” help generate and test hypotheses of management strategies, and monitor for the presence of adverse effects of mechanical ventilation.

44.7 Patient-Ventilator Interactions in the Hemodynamically Unstable Patient

Initiation of mechanical ventilation can substantially decrease metabolic demands and improve the balance between O₂ delivery and consumption. However, a number of cardiopulmonary interactions are created by the application of positive pressure to the airways that require careful consideration.

44.7.1 Implications for Patients with Congenital Heart Disease

Mechanical ventilation for infants and children with congenital heart disease requires balancing the effect of each intervention on the cardiovascular and respiratory systems. Because of the complex cardiorespiratory interactions and the diversity of congenital lesions, a single, standardized

approach is clearly not possible. Ventilator management should address specific pathophysiologic conditions in an individualized manner.

44.7.2 Cardiopulmonary Interactions of the Right Ventricle

The primary effect of increasing ITP on the right ventricle (RV) is decreased preload. Increasing ITP, in association with the initiation of positive pressure ventilation, is transmitted to the right atrium, which impedes systemic venous return and decreases RV preload (Fig. 44.11). RV stroke volume and, thus, cardiac output subsequently decrease.

In addition, the effects of positive pressure ventilation on RV afterload (i.e., PVR) must be considered. At low lung volume, PVR is high due to hypoxic vasoconstriction and increased torsion of the larger pulmonary blood vessels. As lung volume increases and normalizes, PVR falls as these vessels expand and straighten. Significantly above FRC, increases in lung volume increase PVR due to compression of the intra-alveolar capillaries by the overexpanded alveoli (Fig. 44.12). As ITP and lung volume are manipulated, PVR changes, leading to variable effects on RV afterload and, subsequently, RV output and global cardiac output.

In patients with clinically significant pulmonary hypertension, the management goal is to

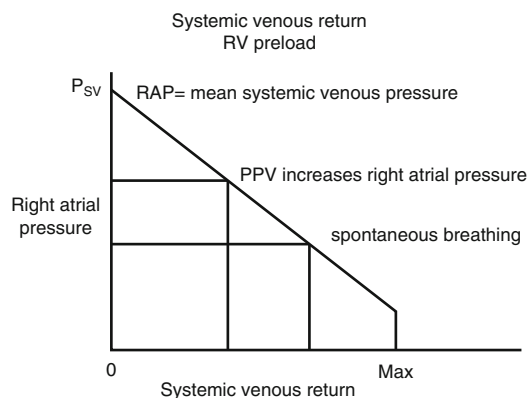


Fig. 44.11 Venous return curve. Right ventricular preload as a function of systemic venous return

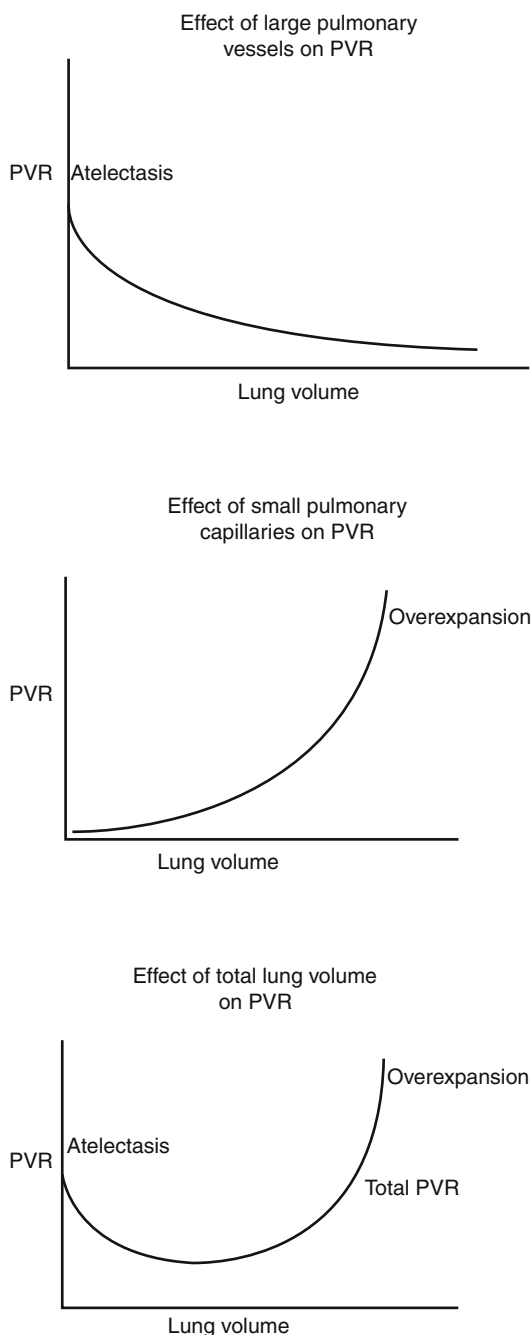


Fig. 44.12 Pulmonary vascular resistance curves. The change in pulmonary vascular resistance with change in lung volume

decrease RV afterload. Ensuring adequate RV coronary perfusion is essential as RV perfusion occurs primarily during systole (Vlahakes et al. 1981); thus, these patients frequently require ino-

tropic agents to augment systemic systolic blood pressure. However, the primary management strategies to improve RV output for these patients must be directed at decreasing the elevated PVR (i.e., RV afterload) by increasing pH, PaO_2 , and PAO_2 , optimizing lung volume, and potentially administering inhaled nitric oxide (Custer and Hales 1985; Drummond et al. 1981; Drummond and Lock 1984; Malik and Kidd 1973; Koehler et al. 1983). The administration of inhaled nitric oxide is beyond the scope of this chapter and is described elsewhere in this textbook.

44.7.3 Left Ventricular Interactions

Positive pressure ventilation can also significantly impact left ventricular (LV) performance. Decreased RV stroke volume, ventricular interdependence, and direct LV compression likely contribute to a decrease in LV preload as ITP increases. On the other hand, LV preload may be augmented in the setting of positive pressure ventilation via the “thoracic pump” mechanism, although clinically significant only at tidal volumes much greater than those currently recommended (i.e., $> \sim 12$ ml/kg). As ITP increases, pressure in the pulmonary vasculature exceeds left atrial pressure, creating a gradient that augments left-sided preload and cardiac output. Given the tidal volumes required, along with the diminishing effect when this strategy is employed over multiple cardiac cycles, thoracic pump augmentation for LV preload can no longer be recommended.

In addition, LV afterload decreases with positive pressure ventilation through an intricate interaction between ITP, myocardial wall tension, and aortic autoregulation. These interactions decrease LV afterload and, thus, potentially increase cardiac output. This beneficial physiologic impact on the left ventricle can be an important consideration when deciding to initiate positive pressure ventilation in the setting of impaired myocardial performance (e.g., cardiomyopathy, myocarditis) and should also be considered when patients with LV dysfunction/failure are being evaluated for an extubation trial.

44.8 Overall Approach to the Hemodynamically Unstable Patient

Respiratory interventions are not always benign and may result in significant adverse effects as described throughout this chapter. Mechanical ventilation should meet the specific goals for an individual patient while minimizing any deleterious effects.

The overall approach to mechanical ventilation should have three basic goals: (1) optimize O₂ delivery by optimizing arterial O₂ content and cardiac output, (2) decrease O₂ requirements of the respiratory muscles (i.e., optimize patient work of breathing), and (3) provide adequate exhalation of CO₂. It should be stressed that O₂ delivery should be “optimized,” not necessarily “maximized” as those interventions required to maximize O₂ delivery may carry increased toxicity (and, thus, increased risk) which may outweigh any theoretical benefit (Gattinoni et al. 1995; Hayes et al. 1994; Heyland et al. 1996; Alía et al. 1999).

Essentials to Remember

- Routine analysis of ventilator waveforms is an essential element of optimizing mechanical ventilatory support.
- Airway scalars graphically depict a variable (pressure, flow, or volume) over time, and airway loops depict variables compared to one another.
- Inadequate ventilation and CO₂ clearance is a common reason for failure to wean from mechanical ventilation and may be secondary to a wide range of etiologies.
- The ratio of physiologic dead space to tidal volume (V_D/V_T) is an important parameter to follow in patients with respiratory failure.
- Respiratory acidosis is caused by CO₂ retention and may be secondary to either decreased ventilatory capacity or increased respiratory muscle load.

- Patient-ventilator dys-synchrony occurs when a patient’s spontaneous effort is not in phase with the positive pressure breaths of the ventilator, and may be due to either trigger or flow insensitivity.
- Optimizing PEEP is essential to the management of patients with acute lung injury to maintain alveolar recruitment.
- Graphical analysis can assist in the diagnosis of airway obstruction of large or small airways in mechanically ventilated patients.
- Pressure-volume loops may demonstrate pulmonary overdistension, which is defined as compliance of the last 20 % of the inspiration being less than the compliance of the total breath ($C_{20}/C_{total} < 1.0$).
- Positive pressure ventilation has a number of complex actions on hemodynamics, one of which includes decreased right ventricular preload.
- Pulmonary vascular resistance is influenced by lung volume and is optimized (minimized) at FRC, with increased resistance at both lower and higher lung volumes.
- As gas exchange parameters are optimized using mechanical ventilation, the impact on hemodynamics should be carefully considered.

Conclusions

Ventilatory management requires a detailed understanding of the dynamics of respiration, airway graphics, and cardiorespiratory interactions. Utilizing the principles of cardiac function, respiratory physiology, and cardiorespiratory interactions, a management strategy can be developed, which matches physiology and pathophysiology for each individual patient. Overall, an optimal ventilatory approach meets the clinical needs of the patient, provides the greatest benefit with the lowest risk for complication, and is a strategy which is familiar to the multidisciplinary ICU team.

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Part XVI

Practical Goal-Directed Approach to Nonconventional Mechanical Ventilation

Educational Aims

- To learn how to choose mean airway pressure and amplitude after intubation or when transitioning from conventional to HFOV
- To learn how to adjust ventilator settings (mean airway pressure, amplitude and frequency) in various pathologies
- To understand benefits and limitations of respiratory monitoring during HFOV

45.1 Initiating HFOV in Neonatal Respiratory Failure

Peter C. Rimensberger

45.1.1 Indication and General Considerations

The classical approach was to consider to switch the patient to HFOV when conventional modes of ventilation fail to provide adequate oxygenation or adequate alveolar ventilation (i.e. rescue HFOV) in infants with respiratory distress syndrome given the more recent understanding that “non-lung-protective” mechanical ventilation, large tidal volume ventilation and/or high peak pressure ventilation or probably more high peak to PEEP pressure swings can cause or worsen lung injury in the experimental setting within a short time period (Bjorklund et al. 1997; Dreyfuss et al. 1985; Ito et al. 1997; Tremblay et al. 1997). Therefore, to initiate any lung-protective ventilator strategy from birth and/or immediately after intubation sounds reasonable. Clinical experience and recent meta-analytic data suggests strongly that initiation of HFOV relatively early in the course of evolving lung disease (Cools et al. 2010; Henderson-Smart et al. 2007) would lead to favourable outcome. A relative risk reduction (RRR) for development of chronic lung disease at 36–37 weeks postmenstrual age of 10 % in favour of elective HFOV (absolute risk reduction (ARR) of 4 %, number needed

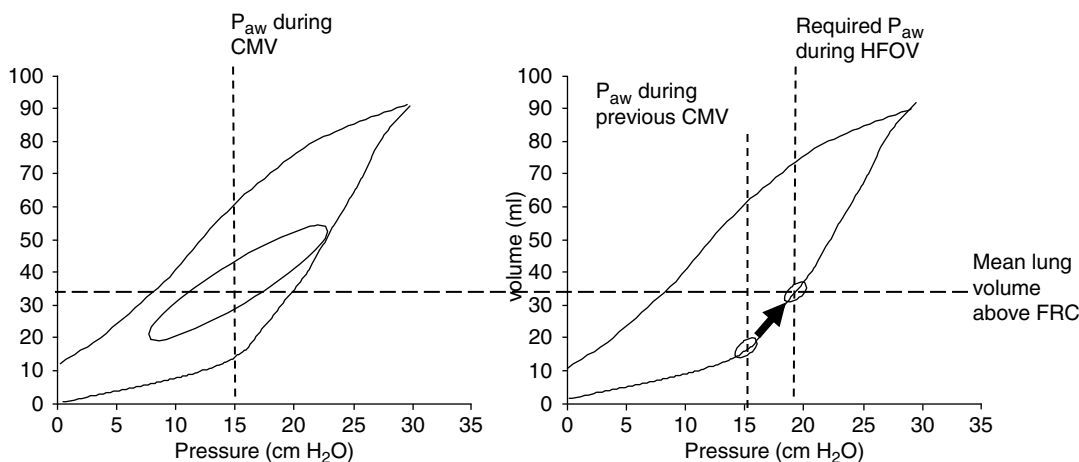


Fig. 45.1 To restore loss in mean lung volume and therefore oxygenation when switching from CMV to HFOV, the mean P_{aw} has to be increased by 3–4 cm H₂O

to treat (NNT) 25) has been demonstrated in a recent meta-analytic review (Henderson-Smart et al. 2007). Furthermore, using HFVO from intubation together with deliberate lung volume recruitment manoeuvres has been reported in a observational study to have excellent outcome (Rimensberger et al. 2000).

Classical indications for HFOV in the neonatal population are infant respiratory distress syndrome; congenital diaphragmatic hernia, usually associated with alveolar and pulmonary vascular hypoplasia (Nobuhara et al. 1996); air-leak syndrome such as pneumothoraces or interstitial emphysema; and persistent pulmonary hypertension of the newborn (PPHN).

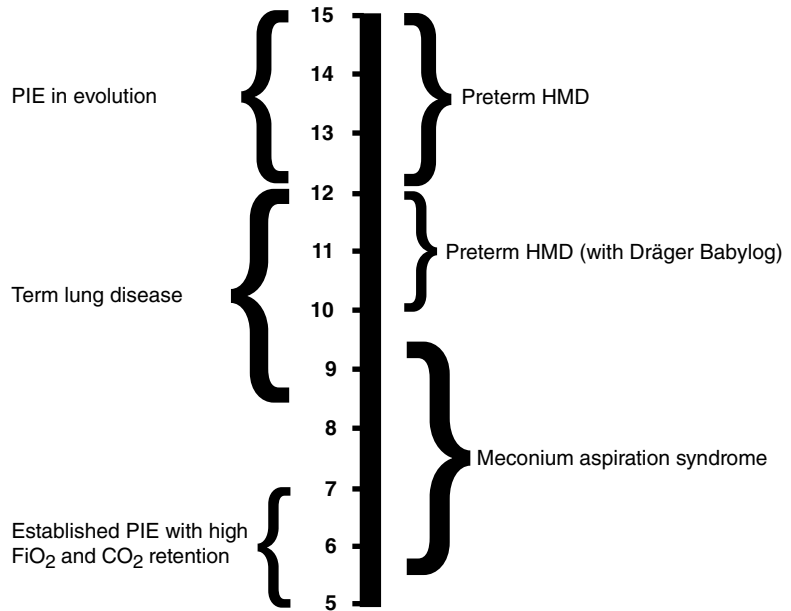
45.1.2 Initial Settings on HFOV

When initiating HFOV directly from intubation (“first intention approach” (Rimensberger et al. 2000)), mean airway pressures (P_{AW}) have to be chosen low (i.e. 6–8 cm H₂O) and followed according to the underlying pathology by a slow stepwise increase in CDP when oxygen requirements are high ($FiO_2 > 0.4$). When transitioning the patient to HFOV from CMV, the P_{AW} is typically set 3–4 cm H₂O above the mean airway

pressure last used on the conventional ventilator to match previous oxygenation. This can be explained by the fact that during HFOV, because of the small pressure swings, the recruitment effect of the tidal breath (or of the positive inspiratory pressure) on CMV (Richard et al. 2001) will get partly lost resulting in hypoxaemia (Fig. 45.1).

Amplitude is initially set by adjusting the pressure swings amplitude to observe visible chest wall vibrations, although it is difficult to define how much is visible enough. A simple method at bedside, at least in the premature infant, is to use two fingers, one positioned on the upper left and the other simultaneously on the upper right chest, and feel the intensity and symmetry of vibrations. This method allows to detect easily one-sided intubation and can become, for an experienced physician or nurse, a simple tool for titration of initial amplitude settings. The adequacy of the chosen pressure amplitude has to be controlled rapidly by a pCO_2 measurement (eventually by transcutaneous measurements) especially in the preterm infant to avoid as possible any hypocarbia that is undesirable because of increasing the risk of cerebral adverse outcome (Giannakopoulou et al. 2004; Blumenthal 2004). Clinically and in absence of heavy sedation that is usually not

Fig. 45.2 Recommended initial frequency ranges for various neonatal pathologies (Courtesy from Peter Dargaville, Hobart, Australia)



needed in neonates while on high-frequency oscillation, the observation that the baby has spontaneous breathing efforts is reassuring because it is unlikely, in absence of major metabolic acidosis, that the baby is over-ventilated at this moment. In fact, neonates can breathe spontaneously during HFOV, the relative high bias flow of the various available neonatal HFOV machines allowing for it (van Heerde et al. 2006).

In actual clinical application, initial frequencies are mainly chosen according the age of the patient and the clinical pathology (Fig. 45.2). Although such an approach is pragmatic and would be easy to use at bedside, it cannot always be fully recommended. Because of the concept of corner frequency of the lung, low-compliance lungs are optimally ventilated at rather high frequencies, while lower frequencies are more appropriate in high-resistance systems (see Sect. 8.2.1.1.1.2) (Pillow 2005; Venegas and Fredberg 1994). In such, using the maximum amplitude coupled with the highest frequency affordable to achieve acceptable CO_2 values independent of age is, in restrictive lung disease (i.e. lungs with poor compliance), the best approach (Bryan and Cox 1999; Fessler et al. 2007).

Therefore, since most of neonatal lung pathologies are characterised by low-compliance lungs associated to or not increased airway resistance, it is hardly necessary to lower frequencies below 10 Hz in neonates.

45.1.3 Adjusting Ventilator Settings During HFOV

During HFOV oxygenation and ventilation can be under normal conditions separated, the mean airway pressures (P_{AW}) being directly related to lung volumes and therefore oxygenation, as long as there is reversible intrapulmonary shunt. Amplitude and frequency changes, in order of priority, have to be used for modifying ventilation efficiency (i.e. CO_2 washout). Alveolar minute ventilation is a function of rate (in Hz) and the squared tidal volume (in ml) ($V_{\text{CO}_2} = f \times V_t^2$). However, the two parameters are not independent from each other. Frequency controls the time allowed (distance) for the piston or membrane to move. Therefore, the lower the frequency, the greater the volume displaced, and the higher the frequency, the smaller the volume

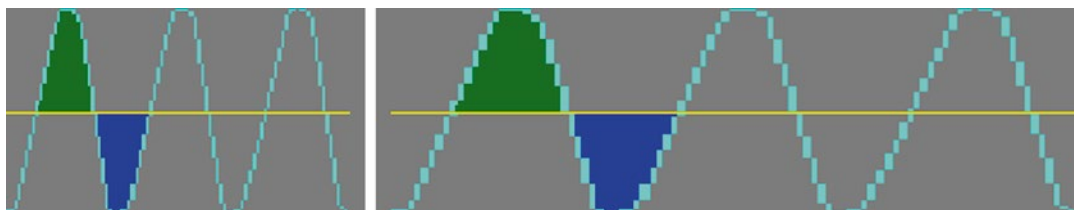


Fig. 45.3 Frequency controls the time allowed (distance) for the piston to move. Therefore, the lower the frequency, the greater the volume (indicated by the area under the

curve) displaced, and the higher the frequency, the smaller the volume displaced

displaced (Fig. 45.3). In consequence, to increase CO_2 washout the amplitude has to be increased, and if this is insufficient, the frequency has to be lowered.

45.1.4 Respiratory Monitoring During HFOV

Because of the oscillatory pressures, swings accelerated molecular diffusion along the airways with a very efficient CO_2 washout during HFOV, and continuous pCO_2 monitoring becomes an obligation during HFOV, especially in the premature infant. With the disappearance of intravascular fibre optic small catheters that allowed for continuous blood-gas measurements, the only method that still can offer such continuous monitoring is transcutaneous pCO_2 monitoring. Despite important technical evolution of this method recently, a certain offset between real PaCO_2 and TCO_2 is often observed (depending from skin perfusion and heating capacity of the sensor). Although this might be seen as a major inconvenience, it does not question the usefulness of continuous tcPCO_2 measurements at bedside, since the offset remains stable over several hours as long as the measuring site or the sensor temperature is not changed. Therefore, trend monitoring is feasible over time and important, since every change in amplitude and/or CDP may induce a rapid change in pCO_2 values (Fig. 45.4) that would be missed by doing a blood-gas measurement only 20–30 min after a change of a ventilator setting, as classically recommended in clinical practice. End-tidal CO_2 measurements cannot be used during HFOV.

45.1.5 The Use of HFOV in Various Pulmonary Pathologies of the Newborn

45.1.5.1 Infant Respiratory Distress Syndrome (iRDS)

For improving oxygenation in a recruitable lung, iRDS being the optimal example for a highly recruitable lung pathology, at least in the early stage of iRDS before widespread formation of hyaline membranes, cellular infiltrations and fibrinous depositions occur, and if applying an “open-lung” strategy, mean airway pressures (P_{AW}) are gradually increased by steps of 1–2 cm H_2O with the goal of reducing the FiO_2 to ≤ 0.4 while achieving adequate SaO_2 values ($\geq 90\%$, and $\geq 85\%$ in the premature infant). During this phase, CO_2 and haemodynamics should be carefully monitored, and at the occurrence of a minimal increase of CO_2 (indicating beginning overdistention) or a decrease of blood pressures (i.e. more than 2 mmHg in the preterm infant), airway pressures have to be reduced despite eventual still poor oxygenation and high FiO_2 needs, before eventually further increasing airway pressures again. Once appropriate saturation is achieved and FiO_2 could be lowered to ≤ 0.4 (e.g. in experienced hands ≤ 0.3), airway pressure should be reduced stepwise in increments of 1–2 cm H_2O (moving downward on the deflation limb of the PV-curve that exhibits hysteresis (Bryan and Cox 1999; De Jaegere et al. 2006; Pellicano et al. 2009)) as long as SaO_2 can be maintained, the ultimate goal being to find the lowest pressure needed to maintain “good” saturation (Fig. 45.4). Chest radiography is usually recommended after finding the “optimal” mean

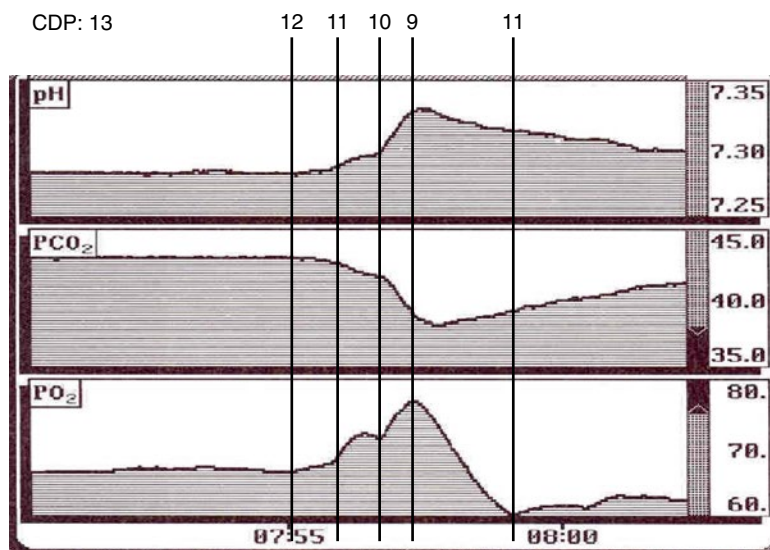


Fig. 45.4 Continuous intra-arterial blood-gas monitoring from a VLBW infant with a “stable” respiratory condition according blood-gas readings. A stepwise reduction of the CDP from initially 13–10 cm H₂O (without any frequency or amplitude change on the high-frequency oscillator, Sensormedics A) leads to a rapid (!) drop in PaCO₂ and an increase in PaO₂, suggesting that 13 cm H₂O of CDP had led to significant lung overdistention. When reducing

CDP one step further from 10 to 9, a sudden drop of paO₂ and a rapid increase in PaCO₂ can be observed, indicating that progressive lung closing starts to happen at this pressure level (i.e. closing pressure). Reincreasing the CDP by 2 cm H₂O to 11 cm H₂O seems not to be enough to re-recruit the lung sufficiently again. After re-recruitment the “optimal CDP” (i.e. lowest pressure that allowed to prevent lung collapse) for this patient was 10 cm H₂O

airway pressures (P_{AW}) to ensure adequacy of lung recruitment and to exclude signs of overinflation, although only gross overinflation can be seen on chest X-ray by the loss of the dome shape of the diaphragm. If signs of overinflation are present, airway pressures have to be reduced further. The common definition of a good lung volume by the position of both hemidiaphragms at the level of the 8th to 9th rib lacks any scientific evidence.

45.1.5.2 Meconium Aspiration Syndrome (MAS)

Meconium aspiration syndrome is characterised by a variable combination of atelectasis, air-flow obstruction and lung inflammation, and is often accompanied by pulmonary hypertension. Maldistribution of ventilation and aeration is therefore common (Yeh 2010), rendering usually efficient but lung-protective ventilation difficult with conventional ventilation. Interestingly, HFOV (see Sect. 47.2.3 for indications) allows often to achieve relative good pulmonary

ventilation and gas exchange (Clark et al. 1994) reducing the need for extracorporeal membrane oxygenation (ECMO) treatment and decreasing the incidence of air leaks.

With poor oxygenation due to an important intrapulmonary shunt (predominant atelectasis), stepwise lung recruitment attempts as described above are justified and relatively high mean airway pressures (P_{AW}) might be required, whereas with poor oxygenation because of an extrapulmonary right to left shunt (with suprasystemic pulmonary artery pressures due to acidosis – acidosis being an important pulmonary vasoconstrictor) and/or lung overdistention, high mean airway pressures or formal recruitment attempts are often inefficient and may be in fact dangerous. This is because of the risk of further overdistending the lungs and often poor haemodynamic tolerance (drop in systemic blood pressure and often oxygenation, as well as the risk of exacerbating pulmonary hypertension). In any case, after any recruitment attempt, whether beneficial or not in terms of oxygenation and ventilation

efficiency, airway pressures have to be immediately lowered to the lowest pressure needed to maintain adequate lung volumes. Because of the high probability of having to deal with high airway resistance, low frequencies below 10 Hz can in general be advocated (Hachey et al. 1998). For more detailed informations on MAS, see Sect. 47.2.3.

45.1.5.3 Lung Hypoplasia

Lung hypoplasia syndromes, of which congenital diaphragmatic hernia (CDH) is part of (see Sect. 47.2.4), are characterised by a reduced total lung capacity in relation to body weight. This means that using “only” 4–5 ml/kg of tidal volume (V_t) during conventional ventilation might be inappropriately high and is likely to cause secondary lung injury. However, using lower V_t than 3–4 ml/kg will render ventilation in terms of CO_2 washout difficult and not be clinically acceptable in a situation when important respiratory acidosis (i.e. permissive hypercapnia) might haemodynamically not well be tolerated because of already coexisting pulmonary hypertension. To switch to HFOV as an early intervention or even first intention approach as soon as PIP exceeds 25 cm H_2O during conventional ventilation has therefore to be proposed. However, to use a high lung volume approach as commonly recommended during HFOV would be inappropriate since lung hypoplasia syndrome does, like CDH, not represent per se a recruitable lung. The peak-to-peak pressures (amplitude) are adjusted to achieve a PaCO_2 in the range of 35–45 mmHg with a pH in the range of 7.35–7.45 as long as the preductal SaO_2 is $>85\%$. Mean airway pressure is limited in absence of any additional restrictive lung disease (e.g. iRDS) to 14–16 cm H_2O .

45.1.5.4 Air-Leak Syndromes

HFOV was established years ago as the choice of a ventilator mode (i.e. rescue treatment) for pre-existing pulmonary air-leak syndromes (PAL) resulting from injurious mechanical ventilation. This was mainly based on a single uncontrolled rescue study (Clark et al. 1986). Furthermore, the use of HFOV was shown to reduce the risk [RR 0.73 (0.55, 0.96), RD -0.174 (-0.321, -0.027),

number of infants that need to be treated (NNT) 6 (95 % CI 3, 37)] of developing any new pulmonary air leak (interstitial pulmonary emphysema and/or pneumothorax) in infants ventilated for severe RDS (Bhuta et al. 2001). However, this latter analysis is based on the results of a single randomised controlled trial (HiFO Study Group 1993), and no benefit of HFOV was shown for those infants with established moderate to severe PIE at entry into the trial.

While HFOV might be accepted as a suitable rescue ventilation mode for PAL, the selection of oscillatory frequency is an unresolved issue: selecting the wrong frequency can potentially exacerbate the underlying problem of air leak. In an optimal setting, frequency would be determined by measuring the impedance of the lung and determination of the corner frequency, which defines the optimal frequency in the overdamped newborn lung (Pillow 2005; Venegas and Fredberg 1994). However, as this approach is currently only used in a research setting, clinicians have little to guide them on optimal frequency selection. In general, increased resistance will decrease the corner frequency, whereas decreased compliance will increase the corner frequency. Corner frequency is also dependent on patient size and is higher in smaller infants. Whereas some advocate using a low HFOV frequency for air leak, there are two major concerns with this approach. Firstly, by using a fixed % setting of inspiratory time, the inspiratory time will increase as frequency decreases – so the duration of exposure to the high pressure is longer and higher tidal volumes will be delivered. Secondly, lower resistance and inertance at lower frequency results in a higher percentage of the airway-opening pressure amplitude being delivered to the proximal and distal airspaces (see Sect. 5.2.1.1). Although the higher respiratory resistance in PAL potentially justifies a lower frequency compared with a poorly compliant lung (i.e. classical iRDS), decreasing frequency below 8–10 Hz is probably not justified based on respiratory mechanics (except in very big infants). Excessively low frequencies potentially expose the central airways to large-pressure oscillations as well as those airspaces proximal to areas of

high peripheral resistance. Decreasing the % inspiratory time to 30 % or below to limit delivered tidal volume would reduce volutrauma associated with the use of lower frequencies.

For setting the mean airway pressure (synonym: continuous distending pressure (CDP)), the clinician needs to consider whether there is associated atelectasis (e.g. in the situation of IRDS) or whether it is solely gas trapping. In the presence of atelectasis and poor oxygenation secondary to intrapulmonary shunt, a recruitment approach by a careful but stepwise increase in CDP is justified. However, as soon as oxygenation improves, CDP should be reduced to the lowest affordable level (according the open-lung concept) while accepting, if necessary, increased oxygen needs ($\text{FiO}_2 > 0.3$) in order to minimise airway pressures as much as possible. If a chest tube is in place, CDP can be titrated downward after a formal recruitment, to the point when air bubbling stops. This low pressure level should be maintained for at least 24 h before the lung is cautiously reinflated. It is important to recognise that in severe persisting or progressive PAL, there is a fine balance to be achieved between stenting of the airways (via maintaining a sufficient CDP) to avoid formation of choke points in the collapsible airways and the benefits of allowing the lung to collapse for 24–48 h as long as the FiO_2 can be kept ≤ 0.6 to achieve acceptable oxygenation. Oscillatory amplitudes should be minimised to reduce cyclic variations in pressure and volume, accepting a PaCO_2 of 45–60 mmHg. Adequate sedation of the infant to avoid active expiration against the oscillatory flow is important. However, paralysis is ideally avoided to minimise the risk of developing paralysis associated with ventilator-induced diaphragmatic dysfunction that might further impede recovery and prolong the need for ventilation.

45.1.6 Weaning from HFOV

Direct weaning from HFOV to CPAP is feasible in most newborns (van Velzen et al. 2009). While reducing repeatedly oscillation amplitudes while having low oxygen needs at low CDPs (around

8 cm H_2O), the baby will take over more and more of the respiratory work by his own spontaneous breathing efforts. As a general rule, it can be said that before extubation, the baby should be at low settings (P_{AW} and amplitude, the latter being dependent from the frequency used) and maintain with such low settings acceptable pCO_2 levels at a normal breathing rate for age, without presenting any major signs of increased work of breathing. A short disconnection of the endotracheal tube from the ventilator should not lead to a desaturation episode, proofing that the baby can maintain adequately a sufficient functional residual capacity (i.e. a stable lung without an increased tendency for collapse). If these conditions are fulfilled, extubation to CPAP can be considered.

Transition to CMV is an alternative and is certainly recommended for less experienced care givers. Such transition could be considered once the mean airway pressures (P_{AW}) could be lowered to about 12 cm H_2O , with an amplitude of not much more than the double of the amplitude value (at appropriate frequency for age), and the baby shows spontaneous breathing efforts. The FiO_2 should be below 30 % at these settings. When switching to CMV, a PEEP level of 5 would be recommended, and the plateau pressures should not exceed 20 cm H_2O for adequate tidal volume delivery of about 5–7 ml/kg.

Essentials to Remember

- Initial mean airway pressure on HFOV is usually set 3–4 cm H_2O higher than the last mean airway pressure during conventional ventilation.
- Most of neonatal lung pathologies are characterised by low-compliance lungs associated to or not increased airway resistance. Therefore, it is hardly necessary to lower frequencies below 10 Hz in neonates.
- Continuous monitoring of CO_2 (transcutaneous pCO_2) should be a standard procedure during HFOV.

- In the search for optimal lung volumes, the use of chest X-ray is of poor value, whereas an incremental/decremental MAP approach combined with continuous monitoring of oxygenation, CO₂ and blood pressure is helpful.
- Allowing for spontaneous ventilation during HFOV is possible in neonates and should always be allowed for.

45.2 Paediatric HFOV

Gerhard K. Wolf and John H. Arnold

Educational Goals

- Initial settings of mean airway pressure, FiO₂, amplitude and device frequency
- The influence of mean airway pressure on alveolar recruitment and oxygenation
- The effect of device frequency and amplitude on alveolar ventilation during HFOV
- How delivered tidal volumes are affected by HFOV settings
- Transitioning the patient from HFOV to conventional ventilation

45.2.1 Initial Ventilator Settings During High-Frequency Ventilation

To improve alveolar recruitment upon the transition to HFOV, the initial mean airway pressure on HFOV is usually set 5–10 cm H₂O higher than the last mean airway pressure during conventional ventilation. If necessary, the mean airway pressure is then increased further by increments of 1–2 cm H₂O until arterial oxygenation improves. A chest radiograph is taken no later than 1 h after transitioning to HFOV to confirm adequate lung expansion and prevent inadvertent hyperinflation. Hyperinflation is

manifested by lung expansion of more than 9 ribs (posterior) and flattened diaphragms. The FiO₂ is usually set at 1.0 upon the transition to HFOV and gradually weaned to 0.6 over time. It is generally accepted that paediatric patients require lower frequencies than neonatal patients. In general, the highest possible frequency that produces adequate ventilation should be chosen, since delivered tidal volumes during HFOV are reduced at higher frequencies, adding to improved lung protection (Hager et al. 2007; Sedeek et al. 2003). In our institution, patients weighing 10–15 kg receive an initial frequency of 10 Hz, patients from 15 to 25 kg a frequency of 8 Hz and patients above 25 kg are ventilated with an initial frequency of 6 Hz. The amplitude of ventilation is generally increased until there is some visible oscillation of the chest wall. When using the Sensormedics 3100A/B in our institution, we usually start at a power setting (“delta P”) of 5.0 and increase the power as needed following arterial blood gases. The ratio of inspiratory to expiratory time is set at 1:2 (33 % inspiratory time) and only increased if the patient cannot be adequately oxygenated despite maximal mean airway pressures. Increasing the I/E ratio above 1:2 increases alveolar mean airway pressure above the mean measured at the airway opening (Gerstmann et al. 1990).

45.2.2 Management of Gas Exchange During High-Frequency Ventilation

45.2.2.1 Mean Airway Pressure, Endotracheal Tube Size and I/E Ratio

Optimal lung volume during HFOV has been described as the lowest mean airway pressure that achieves oxygenating efficiency and maintains lung volume once the lung has been adequately recruited (Brazelton et al. 2001). An increase in mean airway pressure during HFOV is achieved by narrowing the orifice of the expiratory valve or by increasing the bias gas flow.

Mean airway pressure and pressure amplitude are significantly altered by the size of the

endotracheal tube (Gerstmann et al. 1990), and distal airway pressures vary in response to changes of the ratio of inspiratory to expiratory time (I/E ratio) during HFOV. Decreasing the size of the endotracheal tube leads to a decrease of the peak-to-trough pressure amplitude. Data from animal models using alveolar capsules indicate that mean airway pressure is inhomogeneously distributed throughout the lung. Air trapping occurs if the inspiratory time is increased at the expense of the expiratory time. Data from animal models further suggest that distal alveolar pressures can exceed proximal mean airway pressures during I/E ratios of greater than 1:2 (Gerstmann et al. 1990; Allen et al. 1985, 1987). This phenomenon has led to the recommendation that I/E ratios be limited to 1:2 in the clinical setting.

45.2.2.2 Alveolar Ventilation and the Interaction of Rate and Tidal Volume

Several investigators have shown that alveolar ventilation is a function of the rate of oscillations and the squared tidal volume ($V_{\text{CO}_2} = f \times V_t^2$) (Van de Kieft et al. 2005; Courtney et al. 2002). Tidal volume contributes more to CO_2 elimination than frequency, as tidal volume is squared in the formula. The relation between alveolar ventilation and tidal volume is further complicated by the branching generations of the tracheobronchial tree. In experimental studies using fluid models of branching tubes, the oscillatory diffusivity has been described as $D_{\text{osc}} = f^{0.9} \times V_t^{2.2}$ and $D_{\text{osc}} = f^{1.4} \times V_t^{1.8}$ (Kamitsuka et al. 1990; Boynton et al. 1989). In the clinical setting, it is appropriate to estimate alveolar ventilation as a product of the device frequency and the square of the delivered tidal volume.

Any manoeuvre that alters tidal volume will alter CO_2 removal. Increasing the amplitude leads to increasing tidal volumes and improves CO_2 elimination. Conversely, decreasing the amplitude decreases CO_2 elimination by directly decreasing delivered tidal volume. Decreasing frequency also improves CO_2 elimination by increasing delivered tidal volumes. Conversely, increasing the frequency may decrease CO_2 elimination by decreasing delivered tidal volumes.

45.2.2.3 Delivered Tidal Volumes and the Effect of Respiratory Frequency on Tidal Volumes During HFOV

Tidal volumes are not routinely measured during HFOV; however, the lung-protective effects of HFOV are attributed to the combination of small tidal volumes close to the anatomic dead space combined with aggressive alveolar recruitment (Pillow 2005). Recent clinical data suggest that tidal volume delivery during HFOV may be larger than previously assumed. Tidal volumes as high as 5 ml/kg in children (Sturtz et al. 2008) and 6 ml/kg in adults (Hager et al. 2007), all measured at the airway opening, have been reported during HFOV. While tidal volumes of 6 ml/kg are known to be lung protective during conventional ventilation when compared with tidal volumes of 12 ml/kg (The Acute Respiratory Distress Syndrome Network 2000), it is not clear what the optimal tidal volume target to achieve lung protection during HFOV should be. It is possible that when combined with aggressive volume recruitment, tidal volumes of 6 ml/kg during HFOV may lead to overdistention and augment ventilator-induced lung injury.

During HFOV, the device frequency has a significant effect on delivered tidal volume (Fig. 45.5). With an increasing rate, the inspiratory time is decreased and the oscillations of the piston in the ventilator become less efficient, resulting in decreased delivered tidal volumes. Since tidal volumes are more important for CO_2 elimination than rate, increasing the respiratory rate during HFOV paradoxically diminishes CO_2 clearance. Conversely, decreasing the rate results in more efficient oscillations, larger tidal volumes and improved CO_2 clearance.

It is for that reason that in our institution we continue to increase the device frequency as long as the patient's pH is above 7.35. By increasing the device frequency, tidal volumes are reduced and at least theoretically lung protection is maximised. We typically increase the frequency by 1 Hz up to 15 Hz. If, despite a rate of 15 Hz, the pH remains above 7.35, we decrease the amplitude to further reduce minute ventilation

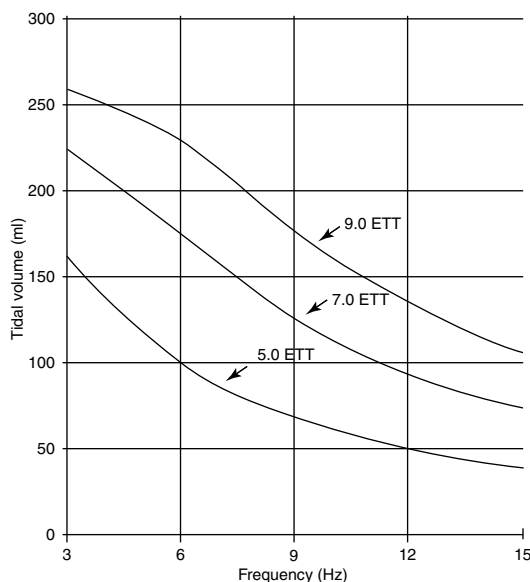


Fig. 45.5 Tidal volumes (ml) and respiratory rate (Hz) during high-frequency oscillation ventilation with the Sensormedics 3100B (Viasys, Yorba Linda, CA). Increasing the rate leads to lower tidal volumes. Note the effect of the endotracheal tube size on tidal volumes (From the Sensormedics 3100B user manual)

45.2.2.4 Effect of an Endotracheal Tube Leak on CO₂ Clearance

Creating an endotracheal tube cuff leak has been suggested as an alternative way to enhance CO₂ clearance in the setting of hypercarbia despite a maximised amplitude and a low rate. The presence of an endotracheal cuff leak may enhance CO₂ clearance by promoting a path of CO₂-egress via a route outside the endotracheal tube. After the endotracheal tube cuff has been deflated to produce a cuff leak, the proximal mean airway pressure will decrease. The expiratory valve or bias flow should be adjusted to maintain the same mean airway pressure in order for this manoeuvre to be effective (Van de Kieft et al. 2005).

45.2.3 Transitioning from HFOV to Conventional Ventilation

Once lung disease is resolving and the gas exchange is improving, the FiO₂ can be gradually weaned to 0.6. We usually do not attempt to wean the FiO₂ to less than 0.6 in the initial

weaning phase. The mean airway pressure should be weaned subsequently by 1–2 cm H₂O at a time. The amplitude of ventilation should be reduced accordingly to achieve clinically acceptable carbon dioxide concentrations. Transition to conventional ventilation should be considered at HFOV settings of a mean airway pressure of 20–25 cm H₂O and a FiO₂ of less than 0.6. An additional indication that the patient is improving may be that the patient is beginning to tolerate suctioning of the endotracheal tube without exhibiting prolonged desaturation indicating lung derecruitment. Whereas neonatal patients can be weaned off HFOV directly (Courtney et al. 2002) and breathe spontaneously on continuous positive airway pressure while remaining on the Sensormedics 3100A, the bias flow of this device is not sufficient to support spontaneous breathing of paediatric patients. Paediatric patients should be transitioned to conventional ventilation from HFOV.

Essentials to Remember

- Initial mean airway pressure on HFOV is usually set 5–10 cm H₂O higher than the last mean airway pressure during conventional ventilation.
- Increasing the MAP increases alveolar recruitment and oxygenation during HFOV.
- Optimal lung volume during HFOV has been described as the lowest mean airway pressure that achieves oxygenating efficiency.
- The amplitude of ventilation is generally increased until there is some visible oscillation of the chest wall.
- Alveolar ventilation is a function of the rate of oscillations and the squared tidal volume ($V_{CO_2} = f \times V_t^2$).
- Possible settings of the frequency: patients weighing 10–15 kg receive an initial frequency of 10 Hz, patients from 15 to 25 kg a frequency of 8 Hz and patients above 25 kg are ventilated with an initial frequency of 6 Hz.

- The highest possible frequency that produces adequate ventilation should be chosen, since delivered tidal volumes during HFOV are reduced at higher frequencies, adding to improved lung protection.
- Transition to conventional ventilation should be considered at HFOV settings of a mean airway pressure of 20–25 cm H₂O and a FiO₂ of less than 0.6.

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Educational Aims

- Outline the general principles of management with HFJV
- Describe practical points essential in managing patients on HFJV, regardless of underlying disease process
- Provide specific guidelines for the management of infants with specific disorders

46.1 General Principles

To make the best use of HFJV, the predominant disease process and pathophysiologic derangement must be used to choose the appropriate ventilation strategy. Where a mixed pathophysiologic picture is present, the clinician must determine the primary and/or most immediately life-threatening problem and focus the strategy on addressing that component first, recognizing that the disease process often evolves rapidly and that the patient's response and the therapeutic approach need to be reevaluated at frequent intervals. The target blood gases, in general, will be

similar to those believed to be appropriate for the patient, regardless of the mode of ventilation. The clinician should beware of the large impact that even relatively small changes in tidal volume can make on alveolar ventilation and take precautions to avoid inadvertent hyperventilation. Continuous pulse oximetry and, if possible, also transcutaneous CO₂ (TCCO₂) monitoring are recommended whenever HFJV is being used. While specific recommendations are provided herein, the clinician should be mindful of individual variation in response and base subsequent clinical decisions on the patient's response and ongoing reassessment of their status. All available information, including physical assessment, blood gas analysis, continuous monitoring, and chest radiographs, need to be utilized to arrive at the most accurate evaluation.

46.1.1 Important Points in the Use of HFJV

1. The standard 15 mm endotracheal tube adapter needs to be replaced with the Bunnell LifePort adapter prior to initiating HFJV. The jet and pressure monitoring lines should initially be capped and then connected to the jet circuit with the ventilator in STANDBY MODE.
2. The endotracheal tube should not be too close to the carina – optimally at least 1 cm above – to avoid inadvertently directing the jet stream preferentially down one or the other mainstem bronchus.

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3. The endotracheal tube should be cut to the shortest practical length to avoid bending and kinking; the ventilator tubing should be supported so as to keep the tube straight.
4. The baby's head must be kept in midline and slightly extended with a shoulder roll, in order to keep the ET tube as straight as possible and optimize penetration of the jet stream down the airways. Allowing the head to be turned to the side results in the jet stream hitting the wall of the trachea, because the ET tube enters the trachea at an angle. This may result in mucosal damage and is certain to reduce the efficiency of gas exchange.

46.1.2 The Importance of Servo Pressure

Servo Pressure is the pressure the ventilator needs to generate in order to deliver the volume of gas across the fixed resistance of the injector cannula and reach the set PIP. When the lungs are atelectatic (i.e., low lung volume), relatively less pressure is needed to fill them and reach the set PIP. With increasing lung volume, more gas needs to be delivered into the lungs before the set PIP is reached; therefore, a higher Servo Pressure is seen. Changes in Servo Pressure are useful in monitoring patient progress and can alert the clinician to important changes in the patient's status. For example, a sudden, large drop in Servo Pressure may indicate a pneumothorax. Increasing Servo Pressure is usually an indication of improving lung volumes, therefore a welcome sign. Conditions that affect Servo Pressure are listed in the Table 46.1.

46.1.3 Suctioning During HFJV

Routine suctioning should be avoided in most patients to avoid loss of lung volume that invariably occurs with disconnection from the ventilator and even closed suctioning systems. In patients who have significant secretions or where there is clinical suspicion of airway obstruction suctioning can be accomplished in two ways. In relatively stable patients, the ventilator can be placed in standby

Table 46.1 Factors that influence Servo Pressure

Servo Pressure increases	Servo Pressure decreases
Improving compliance	Worsening compliance
Increased lung volume	Atelectasis
Improving resistance	Worsening resistance
Leak around ETT	Rt. mainstem bronchus intubation
Leak in the system	Tension pneumothorax
	Secretions in large airways

mode briefly for the duration of the procedure and restarted as soon as completed. The ventilator will take some time to return to the full level of support, which may not be tolerated well in unstable patients. In such patients, it is preferable to suction with the ventilator running. In this case, suction *must* be applied throughout the procedure (during insertion of the catheter as well as its withdrawal), so that excessive pressure does not build up in the airway. Even so, the ventilator may detect excessive pressure and will then open the dump valve, releasing pressure to the atmosphere. A loud click is heard with a brief pause in cycling when this occurs.

46.1.4 Detecting Inadvertent PEEP

When CO₂ retention is unresponsive to an increase in ΔP , especially in a setting where increasing time constants may be present, a decrease in frequency should be considered to eliminate the possibility of inadvertent PEEP due to insufficient expiratory time. In most cases, inadvertent PEEP is detectable by an increase in the monitored PEEP and Paw on the front panel of the ventilator when no increase in PEEP has been made on the conventional ventilator. Normally, V_T does not change with changes in frequency, because the Ti remains constant. Therefore, lowering the HFJV rate should result in an increase in PaCO₂. However, if gas trapping is present, lowering frequency will eliminate auto-PEEP and thus lower the *effective* PEEP, leading to increased ΔP , increased tidal volume, and falling PaCO₂.

46.1.5 Weaning HFJV

The goal is to actively wean the patient toward extubation; patients who are stable within the target ranges for lung inflation and blood gases should have their settings weaned on a regular basis. It is important to balance the desire to wean these patients with the need to avoid causing atelectasis by dropping below the critical closing pressure of the lungs.

FiO_2 should be weaned first in response to good oxygenation. In most cases, mean airway pressure should not be weaned until the FiO_2 is <0.4 . In general, stable patients in the first week or two of life, an attempt should be made to lower mean airway pressure and/or amplitude at least every 6–12 h. Patients that are more chronic may not tolerate as aggressive a weaning schedule. The question of whether patients on HFJV should be switched to conventional ventilation at some point or remain on HFJV until extubation has not been well studied. The only clinical trial which directly addressed this issue was the one by Clark, which demonstrated that infants who were remained on HFOV until extubation did better than infants who were changed from HFOV to conventional ventilation after 72 h (Clark et al. 1992). While there are some advantages to having a patient on conventional ventilation (e.g., tidal volumes can be accurately measured, fewer chest radiographs may be needed, easier to hold the infant), there are few compelling physiologic reasons to change infants from HFJV to conventional ventilation during the acute stage of the disease. It has been the author's practice to wean directly from HFJV to CPAP for many years. Very low birthweight infants can usually be extubated when they have reached PIP of 12–14 cm H_2O , mean airway pressure of 6–8 cm H_2O , and $\text{FiO}_2 \leq 0.25$ –0.30. Older, larger infants can be extubated from somewhat higher settings when they demonstrate good, sustained respiratory effort.

In the following chapter, I will formulate recommendations for the optimal use of HFJV in each of the relevant pathophysiologic conditions previously defined in Part VII of this book, under Clinical Use of HFJV based on a combination of published data and personal experience with

HFJV spanning 25 years. The general strategy is applicable to other HFJV devices, but the specific steps and instructions are based on the functionality of the only widely available HFJV device for newborn infants, the Bunnell Life Pulse jet ventilator.

46.2 Management of Patients with Specific Pathophysiologies

46.2.1 Uniform, Atelectatic Lung Disease

Optimization of lung volume is key to achieving a homogeneously aerated lung, ensuring even distribution of lung volume, reducing exposure to high FiO_2 , preserving surfactant function, and minimizing lung injury (Clark et al. 2000; Froese 1989). Alveolar recruitment maneuvers typically consist of stepwise increases in mean airway pressure. With HFJV, mean airway pressure is controlled primarily by increasing PEEP on the tandem conventional ventilator. PEEP values much higher than those with which many clinicians are comfortable on conventional ventilation are required to achieve adequate alveolar recruitment, because the inspiratory time is extremely short. The need for alveolar recruitment is best judged from a combination of oxygen requirement and chest radiograph.

46.2.1.1 Rescue HFJV in Infants with Atelectatic Lung Disease

When faced with the patient with severe atelectatic lung disease that needs to be transitioned to HFJV in late rescue mode, the clinician must first determine the exact nature of the underlying disease and any coexisting problems, such as PIE or pulmonary hypertension that may require modification of the basic strategy. When transferring from conventional ventilation to HFJV, PEEP should initially be increased by about 2 cm H_2O in order to avoid an inadvertent drop in MAP. When lung volume recruitment is indicated (poor lung inflation, high oxygen requirement), it is most easily achieved by a combination of escalating

PEEP level with conventional ventilator sighs at a rate of 10/min providing the critical opening pressure to achieve alveolar recruitment. Once the lung volume is optimized, the lungs become more compliant, and an effort must be made to lower MAP and stabilize the patient at a point just above the critical closing pressure on the expiratory limb of the pressure-volume loop.

The basic steps are as follows:

1. The default jet rate of 420 is appropriate, inspiratory time is 0.02.
2. Begin with PIP value equal to or slightly lower than previously used on conventional ventilation and adjust PIP to achieve adequate chest wall movement.
3. Set background IMV PIP 2–4 cm below the jet PIP, so as not to interrupt the cycling of the jet ventilator with a TI of 0.4 s and rate of 2–5/min.
4. Confirm adequate PaCO₂ with ABG and TCCO₂.
5. Increase IMV rate to 10/min.
6. Increase PEEP by 1–2 cm H₂O (depending on how high the FiO₂ is) and observe SPO₂.
7. When SPO₂ increases to >93 %, lower FiO₂ as tolerated.
8. Continue to increase PEEP every 5–10 min until (a) the FiO₂ is below 0.40 or (b) there is no further improvement with a 2 cm increase in PEEP and PEEP is at least 10 cm H₂O or the CXR shows hyperinflated lung fields.
9. Monitor TCCO₂ and chest vibration and be prepared to lower jet and IMV PIP quickly, if indicated, to avoid hyperventilation.
10. Once FiO₂ is in target range, drop the IMV rate to 2/min and continue to monitor SPO₂ closely for at least 20–30 min.
11. If SPO₂ starts to drift down, the PEEP is not adequate and needs to be increased further (the IMV sighs were contributing to the MAP, lowering the IMV rate reduces MAP).
12. If the SPO₂ remains in the mid-90s, lower PEEP by 1 cm and observe SPO₂ for at least 20 min.
13. Continue to reduce PEEP in small increments every 10–20 min, as long as SPO₂ remains in the 90s with FiO₂ < 0.40, but do not reduce below 6 cm H₂O.
14. If SPO₂ drops too much, indicating loss of recruitment, briefly increase the IMV rate again and repeat the recruitment process until the target FiO₂ is achieved, then lower PEEP as before, but stop above the point that resulted in de-recruitment.
15. HFJV rate and inspiratory time remain unchanged throughout.

If there is evidence of hemodynamic impairment at any time, lowering the PEEP should be considered, especially if the lung fields are well expanded on chest radiograph. However, it is not uncommon for infants with such severe lung disease to require MAP that is high enough to result in some degree of impairment of venous return and volume expansion is often necessary to maintain stable hemodynamics. A chest radiograph should be obtained following the initial recruitment maneuver and at least daily to detect lung overexpansion that may not be apparent clinically.

46.2.1.2 Elective Use of HFJV in Atelectatic Lung Disease

When initiating HFJV soon after birth, the clinician must choose settings based on clinical impression of the severity of lung disease. The pressure needed with a self-inflating bag or t-piece resuscitator in the delivery room is helpful in selecting the initial PIP. Appropriate PEEP will be determined based on initial oxygen requirement and chest radiograph, if available. The same general approach as described above is used, but more gently, as often these infants do not need aggressive lung volume recruitment.

Specific steps are as follows:

1. The default jet rate of 420 is appropriate; inspiratory time is 0.02.
2. Background IMV rate of 2–5 breaths/min and PIP 3–5 cm H₂O below jet PIP
3. Adjust PIP to achieve adequate but not excessive chest wall movement.
4. If the initial FiO₂ is >0.6, PEEP should be set at 8 cm H₂O and increased, if FiO₂ does not drop below 0.30 within 10–15 min.
5. If the starting FiO₂ is <0.40, PEEP of 6–7 is a good starting point.
6. The goal is to wean FiO₂ below 0.30, because recruitment is much more easily achieved in the first minutes following birth than later on, when atelectotrauma has already occurred.

7. Once FiO_2 is in the target range of <0.30 , cautiously wean PEEP as before, but do not drop below 6 cm H_2O .

The danger of inadvertent hyperventilation is very real soon after birth as a combination of surfactant replacement therapy, clearance of lung fluid, and establishment of good lung aeration all lead to improved lung compliance. Therefore, close monitoring of TCCO_2 values and chest wall movement with aggressive lowering of PIP as needed is essential.

Most commonly, HFJV is used in infants with uniform atelectatic disease, such as RDS in an early rescue mode. While there are insufficient data in the literature to formulate a specific recommendation, most clinicians would consider changing to HFJV when the PIP needed to achieve acceptable PaCO_2 exceeds 25 cm H_2O in infants $<1,000$ g and 30–32 cm H_2O in larger infants (Keszler and Durand 2001). In this situation, the clinician has a starting point based on conventional ventilator settings. The process for transition is similar as with rescue use, but because the severity of illness is not as great, the lung volume recruitment process may not need to be as aggressive. When transferring from conventional ventilation to HFJV, PIP should decrease by 1–2 cm H_2O , while PEEP should initially be increased by about 2 cm H_2O to maintain approximately the same MAP. Subsequently, the need for lung volume recruitment should be determined based on oxygen requirement, blood gas analysis, and radiographic findings. Background IMV should not be higher than 2/min unless active lung volume recruitment is under way. In these less severely affected infants, the goal should be to reduce FiO_2 to <0.30 , a target that should be relatively easily achieved by the procedure described above. Once more, it is imperative to respond in real time to increased chest wall movement and falling TCCO_2 by lowering PIP to inadvertent hyperventilation.

46.2.2 Air Leak Syndrome

HFJV is the preferable ventilation mode for the treatment of significant PIE (Keszler et al. 1991) and severe/recurrent pneumothorax (Gonzalez et al. 1987). In general, as soon as substantial PIE

becomes apparent, steps should be taken to minimize progression and, at the same time, avoid making the underlying problem worse. The severity of PIE on the one hand and the degree of atelectasis on the other will dictate the level of MAP to be used. The older approach of aggressive lowering of MAP has given way to a more balanced strategy that recognizes that atelectasis almost always coexists with PIE and that while the lungs may appear overexpanded due to air trapped in the interstitium, the airspaces are generally under-expanded.

The process for initiating HFJV in infants with PIE or other air leak is as follows:

1. HFJV rate should be no higher than 400/min to allow adequate expiratory time (PIE increases time constants). If PaCO_2 remains higher than desired, a trial of lower rate is warranted and will often result in lower PaCO_2 values.
2. PIP should be decreased by 2–3 cm H_2O to minimize further air leak and allow PCO_2 to rise to maximum acceptable level for the infant's age (50 Torr if <72 h, 55–65 subsequently). Subsequent PIP adjustments are guided by TCCO_2 changes and blood gas analysis.
3. Unless the lungs are grossly overexpanded, PEEP should initially be increased by 1–2 cm H_2O to maintain approximately the same MAP and avoid atelectasis.
4. Subsequently, the need for lung volume recruitment should be determined based on oxygen requirement and radiographic findings as previously described, but with a less ambitious target FiO_2 , typically <0.50 .
5. Background IMV should not be higher than 2/min and should be discontinued, unless active lung volume recruitment is under way.

The presence of PIE should discourage overly aggressive lung volume recruitment, but moderate level of PEEP is essential in preventing worsening atelectasis. To that end, PEEP of 6–8 cm may be appropriate even when mild to moderate PIE is present. However, in general, we accept higher FiO_2 and tolerate higher PaCO_2 values in order to facilitate resolution of PIE. Frequent reevaluation of the situation is necessary to prevent worsening atelectasis or progression of PIE. Chest radiographs should be considered as often as twice daily in this situation. As the balance shifts from

PIE to atelectasis or vice versa, the strategy needs to be altered to address the more prominent problem. Clearly, this situation presents us with a difficult challenge of balancing the opposing imperatives. If the PIE is extensive and the lungs are overexpanded, background IMV should be discontinued, and in all cases, it should be used with caution with a rate no higher than 2/ min.

Treatment of infants with pneumothorax, bronchopleural fistula, and tracheoesophageal fistula follows essentially the same principles. The extremely short inspiratory time and the gas flow pattern in the upper airways favors resolution of fistulae even when relatively high PEEP is needed to maintain lung expansion. The strategy therefore should be directed at the predominant lung pathophysiology, with the same permissive attitude toward FiO_2 and PaCO_2 .

46.2.3 Severe Nonuniform Lung Disease/PPHN

Nonuniform lung disease, such as is present in MAS, presents special challenges to the clinician, because of the highly variable time constants, high airway resistance, and coexisting pathophysiologies, such as air leak and PPHN (Goldsmith 2008). Surfactant inactivation is always a part of the picture; therefore, these lungs tend to have poor compliance, are prone to atelectasis, and benefit from lung volume recruitment. The large size of the patient and the high airway resistance result in prolonged time constants and require lower frequencies to avoid air trapping. Because gross particulate matter in the large airways would break up the jet stream and adversely affect efficacy of HFJV, it is important to suction the large airways well before initiating HFJV.

The steps in initiating HFJV therapy are as follows:

1. Adjust PIP as needed to achieve adequate chest wall movement and adequate PaCO_2 . Avoid hyperventilation even in the presence of PPHN.
2. When changing from conventional ventilation, PEEP should be increased by 2–3 cm H_2O – typical PEEP value is 7–10 cm H_2O .

3. Optimize lung inflation with appropriate increase in PEEP, as needed. In the presence of PPHN, oxygenation may not primarily be a function of intrapulmonary V/Q matching, so care must be taken to use chest radiographs more frequently to guide lung volume recruitment. Both overexpansion and atelectasis increase pulmonary vascular resistance. The goal is to achieve well-aerated lungs with the dome of the diaphragm projecting over the 9th–10th rib posteriorly on a well-centered film. FiO_2 may not be able to be weaned much until associated pulmonary hypertension is successfully treated.
4. Avoid air trapping by setting rate no higher than 360/min (6 Hz), sometimes as low as 280 br./min. If PaCO_2 remains higher than desired, a trial of lower rate is warranted and will often result in lower PaCO_2 values.
5. Treat associated pathophysiologic derangements as needed: volume expansion for functional hypovolemia, inotropic support, sedation, antibiotics for sepsis, etc.
6. Inhaled nitric oxide (iNO) is easily incorporated into the jet ventilator circuit as shown in Fig. 46.1. Please note that adding iNO to the conventional circuit only is NOT adequate.
7. Low rate IMV is appropriate in most instances. Because airways dilate during inspiration, sighs may help aerate parts of the lungs obstructed by meconium in the airways.
8. Be prepared to suction more frequently when HFJV is initiated soon after birth in MAS patients, because the coaxial rotational expiratory flow appears to bring up secretions and meconium.
9. Keep the head in midline and slightly extended with a shoulder roll and make sure the ET tube is not too close to the carina.

It is important to recognize that MAS is a heterogeneous condition, which evolves over time. Airway obstruction usually predominates in the early stages. Although HFJV may facilitate mobilization of secretions, the presence of particulate debris in the large airways may transiently interfere with efficient ventilation-suction.

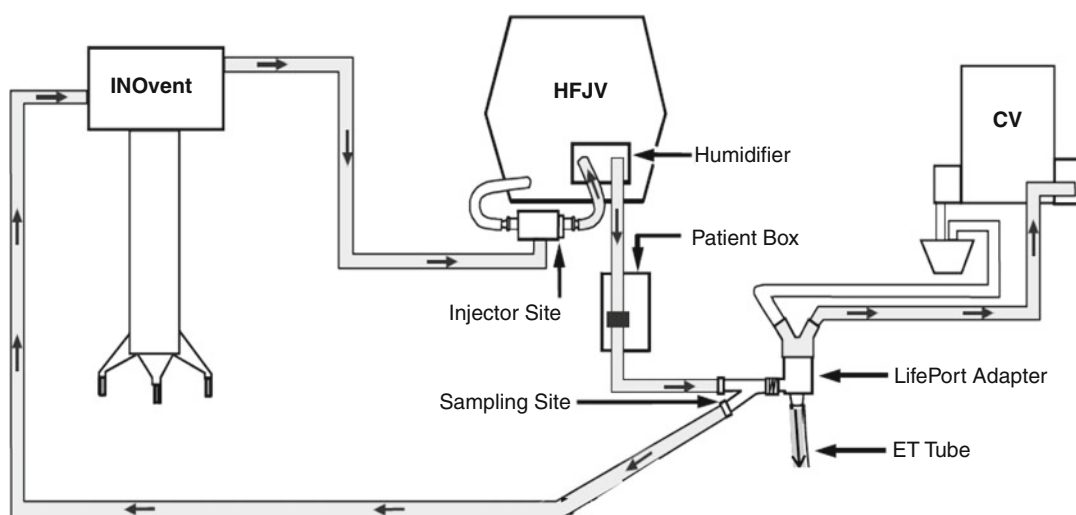


Fig. 46.1 The iNO injector module of the INOmax DS device is spliced into the green tubing of the Life Pulse ventilator circuit between the gas outlet from the ventilator and the humidifier cartridge and a one-way valve is

placed between the injector and the cartridge. The NO sampling line is spliced into the green gas delivery tube between the patient box and the Life Port endotracheal tube adapter

46.2.4 Bronchopulmonary Dysplasia

Infants with BPD also present difficult challenges, regardless of the mode of ventilation. The BPD may develop gradually while the infant has been ventilated with HFJV, or the clinician may elect to change to HFJV from conventional or oscillatory ventilation when the patient is doing poorly. The latter group is typically much more ill, and frequently, these infants are experiencing acute deterioration of their status due to late onset sepsis. In that instance, treatment needs to focus not only on optimizing ventilatory support but also on treating the underlying disease process.

The optimal approach to treating these infants with HFJV has not been systematically studied, and there is great individual variability in each patient's pathophysiology; therefore, it is impossible to provide detailed guidelines for their treatment. Extremely preterm infants with evolving BPD need to have a reevaluation of the appropriateness of their ventilator settings in view of the changing lung mechanics. With increased airway resistance, ventilator rate should come down to 400 or below. Infants with BPD are prone to air trapping not only because of overall increase in airway resistance from inflammation and

increased secretions but also because of airway collapse. Their small- and medium-sized airways are poorly supported because of the simplified lung with decreased alveolization and tend to close at low lung volume, leading to air trapping. The use of oscillatory ventilation with its active exhalation tends to worsen this problem, because the floppy airways with negative intraluminal pressure are surrounded by aerated lung that has a higher pressure; this situation leads to the development of "choke points" (Bryan and Slutsky 1986). HFJV with passive exhalation and the use of adequate PEEP appears to maintain airway patency more effectively. Because of the unique gas flow characteristics of HFJV, distribution of ventilation is relatively independent of regional differences in lung compliance. Optimization of lung volume remains an important goal, but a more difficult one to accomplish than early on in infants with uniform lung disease. Air trapping in infants with BPD is often related to expiratory flow limitation at low lung volumes, because the poorly supported airways collapse as the lung empties (Tepper et al. 1986). When overexpansion of the lungs is seen radiographically, lowering PEEP typically fails to resolve it. Instead, increasing PEEP is often

effective in maintaining airway patency. Permissive hypercapnia is probably appropriate in these infants, who typically are able to develop compensatory metabolic alkalosis.

46.2.5 Restrictive Disease

Restrictive diseases include conditions where external factors (chest wall edema, abdominal distention) or intrathoracic space-occupying lesions restrict lung motion and tidal excursion. The obvious physiologic rationale, supported by limited published data, has made the use of HFJV routine in these relatively common conditions. Most clinicians will turn to HFJV when moderate to high PIP is needed to achieve adequate ventilation or whenever there is evidence of hemodynamic impairment. Aggressive alveolar recruitment is not indicated, but sufficient PEEP needs to be used to maintain adequate lung volume and acceptable V/Q matching. This is especially true when massive abdominal distention is pushing up on the diaphragm, leading to loss of lung volume. Permissive hypercapnia and higher than usual FiO_2 targets are typically accepted in order to mitigate hemodynamic impairment. The clinical benefit is usually quite obvious, and ventilation often improves dramatically, at times leading to inadvertent hyperventilation. Worsening abdominal distention and/or chest wall edema may require subsequent escalation of support. Intravascular volume replacement and other supportive care need to go hand in hand with optimized respiratory support.

46.2.6 Pulmonary Hypoplasia

Infants with pulmonary hypoplasia have small, relatively immature lungs that are very prone to air leak. Because the pulmonary vascular bed is also hypoplastic, pulmonary hypertension is almost always present and often refractory to treatment. Additionally, excessive lung expansion will make the pulmonary hypertension worse.

The optimal strategy has not been well defined, but should be based on the known pathophysiologic features associated with pulmonary hypoplasia.

The specific steps are as follows:

1. Rate of 420–450 is appropriate even in full-term infants, because the time constants are short.
2. Background IMV should be no higher than 2/min and should be discontinued if air leak develops.
3. PIP should be set at the lowest value consistent with acceptable PaCO_2 . Hyperventilation should be avoided.
4. PEEP should be sufficient to achieve adequate lung aeration and expansion (difficult to judge radiographically), but aggressive volume recruitment is not indicated. Typically, PEEP of 6–8 cm H_2O is used, but higher values may be needed in some infants.
5. Oxygenation is often primarily affected by extrapulmonary right to left shunting also limiting the feasibility and the benefit of lung volume recruitment.
6. Frequent chest radiographs are needed to monitor lung volume.
7. Relatively high FiO_2 and mild permissive hypercapnia, even in the presence of PPHN are accepted.
8. PIP and PEEP should be weaned whenever possible to minimize lung injury, the key goal in these fragile infants.

Conclusion

HFJV is an invaluable tool in the treatment of a variety of clinical conditions. Like any tool, it gives the best results when used by an experienced operator who understands the unique characteristics of the device and utilizes it in a manner that will optimally address the specific underlying pathophysiology. While the specific guidelines given above should prove useful in clinical care of patients, it must be remembered that individual infants may respond differently, necessitating careful reappraisal of a chosen strategy, if the response is different from the anticipated course.

Essentials to Remember

- The basic principles of gas exchange are similar to other forms of HFV, but the user must understand the unique aspects of HFJV.
- HFJV requires higher PEEP levels than conventional ventilation to maintain adequate mean airway pressure.
- Improving lung compliance can easily lead to inadvertent hyperventilation; close monitoring of TCCO₂ and rapid weaning of PIP are essential in preventing lung and brain injury.
- Tailoring ventilator strategy to the predominant underlying pathophysiology is essential in optimizing patient outcomes.

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Part XVII

Mechanical Ventilation in Various Pulmonary Pathologies

47.1 Introduction and Definitions

Peter G. Davis

Acute respiratory failure requiring assisted ventilation is one of the most common reasons for admission to the neonatal intensive care unit. Respiratory failure is the inability to maintain either normal delivery of oxygen to the tissues or normal removal of carbon dioxide from the tissues. It occurs when there is an imbalance between the respiratory workload and ventilatory strength and endurance. Definitions are somewhat arbitrary but suggested laboratory criteria for respiratory failure include two or more of the following: $\text{PaCO}_2 > 60$ mmHg, $\text{PaO}_2 < 50$ mmHg or O_2 saturation $< 80\%$ with an FiO_2 of 1.0 and $\text{pH} < 7.25$ (Wen et al. 2004).

Many have observed that neonates are not merely small adults. Infants have less respiratory reserve than older individuals, and respiratory

failure is more common, not only during pulmonary illnesses but also any serious illness. Infants have narrow, compliant airways which are prone to collapse. Their chest wall is not ossified and has low muscle mass. It is very compliant, which in combination with a low functional residual capacity puts the infant at risk of airway collapse and atelectasis. The low recoil of the chest wall means that little pressure is required to expand the chest wall. In contrast to older subjects, the major force contributing to elastic recoil is surface tension at the air-liquid interface in the distal airways and alveoli. Surfactant deficiency, both primary and secondary, leads to decreased stability of the small terminal airways and alveoli and ultimately to collapse.

Assisted ventilation aims to (1) maintain adequate oxygenation, supporting gas exchange by improving alveolar ventilation, (2) restore or maintain functional residual capacity to prevent atelectasis or reopen areas of collapsed lung and

(3) reduce the work of breathing in the presence of high airway resistance and/or reduced compliance. For neonates, the aim is to gently support the patient in order to allow time for the resolution of the underlying disorder without causing further injury through ventilation.

47.2 Pulmonary Pathologies in the Neonate Leading to Respiratory Failure

Louise S. Owen and Peter G. Davis

Educational Aims

- To describe the pathology and physiology of RDS
- To outline the risk factors associated with RDS
- To describe the impact of delivery room and early management of RDS on outcome
- To delineate the range of non-invasive and invasive modes of respiratory support available to treat RDS
- To outline the importance of instituting a lung protective ventilatory strategy to reduce the risk of developing BPD
- To outline the role of additional therapies in the treatment of RDS
- To describe the complications and outcomes of RDS

47.2.1 Infant Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) remains the most common reason for admission to neonatal intensive care and is associated with significant morbidity and mortality (Wen et al. 2004; Horbar et al. 2002). RDS develops due to immaturity of the surfactant synthesis systems, insufficiency of surfactant production and structural immaturity of the lungs.

47.2.1.1 Pathophysiology of RDS

47.2.1.1.1 Lung Development

Human lung development falls into distinct stages: the pseudoglandular stage from 5 to 17 weeks gestation, the canalicular stage from 16 to 26 weeks gestation, the saccular stage between 24 and 38 weeks and the alveolar stage from 36 weeks until 2 years. During the canalicular phase, there is ongoing branching of the respiratory bronchioles with thinning of the airway epithelium, so that by the end of this period there is some capability for gas exchange. During the saccular stage, the peripheral airways widen into saccules which then form the alveolar ducts, the precursor to alveoli. Infants born during this period do not have fully functioning terminal airways; there are fewer, thick-walled gas exchange units. The true alveolar stage does not start until 36 weeks gestation and continues postnatally until about 2 years of age. The development of fully functional alveoli is also dependent on development of the surrounding mesenchyme and the alveolar capillaries.

47.2.1.1.2 Transition

The transition from fetal life to newborn life involves multiple processes. The most important adaptation is the conversion of the lungs from a fluid-filled unit to air-filled spaces, capable of working as a gas exchange organ. In utero, the terminal airways are full of fluid secreted from the pulmonary epithelial cells. This fluid is an important determinant of lung growth. The volume of fluid is equivalent to functional residual capacity (FRC) post delivery. Following delivery, lung fluid is cleared. This process is slower and less efficient in preterm infants (Egan et al. 1984). The sequence of lung inflation, fluid clearance and rising pH controls the early fall in pulmonary vascular resistance and initial oxygenation. The action of the respiratory muscles overcomes the resistive properties of the airways to develop FRC and tidal volume (Sinha et al. 2008). Antenatal, perinatal and resuscitation events interact to affect the processes of lung fluid clearance, FRC development and maintenance of adequate tidal volume.

47.2.1.1.3 Physiology

RDS is characterised by stiff non-compliant lungs with low levels of surfactant. Premature lungs have insufficient alveolarisation, decreased functional surface area, increased distance from alveoli to adjacent capillaries and reduced surfactant synthesis and show less hysteresis than normal lungs. The terminal airways collapse at end of expiration due to high surface tension. Tidal volumes are small and the dead space is relatively large. Infants are able to increase their respiratory rate to compensate for the low tidal volume. This means they may be able to maintain their minute volume, but the work of breathing is doubled (Hjalmarson and Olsson 1974; McCann et al. 1987). Most infants have some surfactant at birth (Reynolds et al. 1968) but levels fall within a few hours as alveolar protein leak inhibits function (Ikegami et al. 1983). Without exogenous surfactant infants tire, minute volume falls and hypoxia and acidaemia follows. This further increases surfactant inhibition.

47.2.1.1.4 Histology

Hyaline membranes are the characteristic histological finding in RDS and have given the disease its alternative name of hyaline membrane disease. In immature, stiff, surfactant deficient lungs, alveolar epithelial cell death starts to occur in the first hour after birth. Dead cells detach from the basement membrane, denuded patches appear, and protein leak leads to interstitial oedema. Hyaline membranes form; they consist of plasma protein, fibrin, cellular debris, red blood cells, macrophages and proteinaceous exudate. The material lines or fills the air spaces inhibiting gas exchange. Most of the protein leak occurs over the first 24 h (Ikegami et al. 1992). During this time the hyaline membranes, which are initially patchy, become more confluent. Ischaemia exacerbates RDS with epithelial necrosis occurring in the terminal airways. Asphyxiated infants have more severe RDS (Linderkamp et al. 1978) and respond less well to surfactant treatment (Skelton and Jeffery 1996).

After 24 h, inflammatory cell numbers increase and macrophages start to ingest the

membranous material. Epithelial regeneration commences after 48 h and surfactant production starts to increase. Microscopically, the surfactant deficient lung is characterised by collapsed air-spaces alternating with hyper-expanded areas, vascular congestion and hyaline membranes. The lungs remain non-compliant and atelectatic until surfactant reappears at 36–48 h (Kanto et al. 1976). Hyaline membranes are broken down by the seventh day but will persist for longer if the infant is receiving mechanical ventilation. Healing is hyperplastic with shedding of the bronchiolar epithelial cells. Proteinaceous material in the terminal airways induces scarring and fibrosis in the developing alveoli and ultimately can lead to bronchopulmonary dysplasia or chronic lung disease (CLD).

47.2.1.1.5 Clinical Picture

The diagnosis of RDS is made on the basis of the clinical picture and the chest x-ray which demonstrates decreased lung volumes and a bell-shaped chest. Uniform infiltrates described as a ‘ground glass’ appearance involve all lobes of the lungs. Air bronchograms are seen as the infiltrate outlines the larger airways that remain air filled. In severe cases, the infiltrates are such that the cardiac and diaphragmatic borders become indistinct giving a ‘white-out’ appearance. Infants increase their respiratory rate, take smaller volume breaths and use accessory muscles to assist with their increased work of breathing. This results in nasal flaring and rib, sternal and subcostal recession. Infants attempt to stop alveolar collapse at end expiration by closing the glottis, resulting in grunting. As the infant tires, cyanosis develops and the infant develops apnoeic episodes with desaturations. Infants with RDS have decreased urine output and commonly become oedematous. The differential diagnosis includes infection (particularly group B streptococcal infection), persistent pulmonary hypertension of the newborn, aspiration pneumonia, lung malformations and upper airway obstruction, transient tachypnoea of the newborn, meconium aspiration syndrome, air leak syndromes, pulmonary haemorrhage, asphyxia, congenital heart disease,

primary neurological or neuromuscular disease and inborn errors of metabolism.

47.2.1.2 Lung Mechanics of RDS

47.2.1.2.1 FRC and Physiological Dead Space

The effects of RDS on lung function vary with gestational and postnatal age. Newborns with normal lungs quickly develop an FRC of about 30 mL/kg (McCann et al. 1987). FRC is the volume of gas remaining in the lungs at the end of normal expiration, preventing alveolar collapse and allowing the lung to operate at optimal efficiency. Less mature infants have lower lung volumes, including a lower FRC; however, tidal volume remains about the same at 4–6 mL/kg (Hislop et al. 1986). These effects proportionally increase the physiological dead space to 60–80 % of tidal volume, compared with 30–40 % of tidal volume in healthy lungs (Avery et al. 1981). To compensate for this increased dead space, infants with RDS increase their respiratory rates. For infants without RDS, a rise in respiratory rate can lead to gas trapping; however, in babies with RDS, an increased respiratory rate may be enough to help maintain necessary FRC and avoid end-expiratory alveolar collapse. Newborn FRC already approaches alveolar closing volume, so a reduction in FRC permits atelectasis to readily develop. Further loss of FRC occurs due to vascular congestion, interstitial oedema and proteinaceous exudates.

Infants with RDS try to preserve lung function by delaying contraction of the diaphragm to delay the loss of thoracic volume and keep the alveoli inflated (Davis and Bureau 1987). Infants also contract the laryngeal muscles to keep the upper airway closed until late expiration, and then when these muscles relax, the abdominal muscles contract. The explosive release of air sounds as a grunt. Grunting helps to delay air escape from the lung and maintains FRC. It has been demonstrated that when an endotracheal tube is inserted, the loss of these mechanisms result in a fall in arterial oxygenation (Harrison et al. 1968). Surfactant treatment helps to increase lung volumes, so that lower positive pressures are required for ventilation. Higher lung volumes

are maintained even when positive pressure is reduced because FRC increases following surfactant treatment (Goldsmith et al. 1991). Most lung volume improvement is seen when exogenous surfactant containing surfactant proteins are used (Rider et al. 1993). As FRC improves oxygenation improves. This normally occurs as lung fluid clears (Engle et al. 1983) or following surfactant treatment (Edberg et al. 1990) or when using distending pressure, such as mechanical ventilation (Richardson and Jung 1978). In an infant with RDS, the FRC returns to normal by about day 7.

47.2.1.2.2 Time Constant, Compliance and Resistance

Infants with RDS have less compliant, more resistant lungs. This results in a short time constant, meaning that gas leaves the terminal airways more quickly than in normal lungs. Surfactant-deficient lungs, with high surface tension in the alveoli, exhibit collapse in expiration of the smaller alveoli. This leads to overdistension of the larger alveoli that have remained open. Compliance is reduced as fewer terminal air spaces are ventilated, and those that are open become overdistended. Alveolar instability affects compliance as the critical opening and closing pressures vary. This means that alveoli open and shut suddenly, smaller ones then stay closed and open alveoli overfill. There is increased resistance in the lungs due to reduced cross-sectional area of the patent airways to the distal lung units. During spontaneous breathing the activity of the respiratory muscles tries to overcome elastic resistance and inertia of the tissues by increasing the change in intrapleural pressure, resulting in distortion of the compliant chest wall. Pulmonary compliance improves more slowly, following surfactant administration, than the rapid improvement seen in FRC (Edberg et al. 1990). This is reflected by quick improvement in oxygenation, compared with the relatively slower fall in carbon dioxide. The reduced compliance slowly returns to normal around day 7.

47.2.1.2.3 Gas Exchange and Shunting

Arterial carbon dioxide levels rise in RDS due to alveolar underventilation from atelectasis and

the proportional increase in dead space. Most hypoxia in RDS is due to right-to-left shunting. Small shunts exist across the foramen ovale (if right atrial pressure is higher than left atrial pressure) and the ductus arteriosus (which is often patent in infants with RDS for 48 h). These shunts only account for about 10 % of the shunt in RDS (Seppanen et al. 1994) and are more important in other lung pathologies such as persistent pulmonary hypertension. In RDS, the most important shunt is intrapulmonary, as capillary blood travels through unventilated, or hypoventilated, atelectatic areas of the lung. Pulmonary arterial pressure normally falls rapidly, to half of the in utero level, soon after birth, but in RDS it can remain high for the first week (Evans and Archer 1991). The pulmonary pressure is proportionately higher in infants with more severe RDS and can exacerbate the hypoxia seen in RDS.

47.2.1.3 Epidemiology of RDS

Risk of RDS varies with lung maturity, which is intrinsically related to gestational age. Lung maturity is altered by the use of antenatal steroids and by postnatal surfactant treatment. Premature infants have lower levels of surfactant, although in almost all infants, there is some surfactant present within a few hours of birth (Reynolds et al. 1968). If newborn infants are not given surfactant, then levels fall as protein leak and oedema increase and the infant tires. The resulting hypoxia and acidosis reduce surfactant synthesis, and the clinical condition deteriorates further.

47.2.1.3.1 Prevention of RDS

Ideally prevention of RDS would focus on avoiding preterm birth. Addressing social deprivation and reducing rates of genital tract infection and preterm rupture of the membranes, both of which increase preterm delivery, could reduce RDS rates. If preterm labour occurs, or maternal disease necessitates preterm delivery, pharmaceutical intervention such as tocolytics may prolong pregnancy for 48 h. This is sufficient time to administer steroid treatment and reduce the risk of RDS. Antibiotics for suspected infection, or for membrane rupture, reduces progression

to preterm delivery (Gomez et al. 1995). Other factors which impact on RDS development include asphyxia and drug depression of the infant. Care in avoiding intra- and postpartum asphyxia and minimal use of maternally administered opiates, anaesthetics, benzodiazepines and magnesium sulphate may also reduce rates of RDS.

47.2.1.3.2 Antenatal Steroids

Synthetic steroids given antenatally as betamethasone or dexamethasone, to women at risk of preterm delivery, reduce rates of RDS (odds ratio (OR) 0.63, 95 % confidence interval (CI) 0.44, 0.82). Neonatal deaths are reduced (OR 0.6, 95 % CI 0.48, 0.75) (Crowley 1995) as are rates of germinal matrix/intraventricular haemorrhage and necrotising enterocolitis (Ward 1994). The widespread uptake of antenatal steroid use has had a dramatic impact on the epidemiology of RDS over the last 20 years. Steroids induce enzymes for surfactant synthesis, induce genes for synthesis of surfactant protein (Mendelson et al. 1993), improve the quality of the surfactant produced (Ueda et al. 1995; Lanteri et al. 1994), mature the lung tissue and increase the number of alveolar divisions (Lanteri et al. 1994). The optimal timing of steroid administration has been shown to be 24–168 h prior to delivery (Crowley 1995). Some benefit can be seen with doses given 4–24 h prior to delivery (Sen et al. 2002). There is limited evidence of benefit below 28 weeks gestation (Garite et al. 1992) or beyond 34 weeks gestation (Liggins and Howie 1972). Steroids appear to be safe in terms of effect on maternal pregnancy-induced hypertension (Lamont et al. 1983), prolonged rupture of the membranes (Crowley 1995) and maternal diabetes. No long-term adverse outcomes have been demonstrated in infants following a single course of antenatal steroids (Dessens et al. 2000).

Repeated courses of steroids continue to improve neonatal outcomes in terms of lung function but may be detrimental to fetal growth and brain function (Aghajafari et al. 2002). A randomised controlled trial (RCT) in Australia demonstrated that repeated doses of antenatal corticosteroids reduced neonatal morbidity, compared with a single course, without changing

neurosensory disability or body size at age 2 (Crowther et al. 2007). Another RCT of repeated versus single-steroid courses found a non-statistically significant increased rate of cerebral palsy in the repeated course group (Wapner et al. 2007); this question warrants further study. A retrospective review of infants who received multiple courses of steroids, compared with infants who received no antenatal steroids, showed that repeated courses were associated with decreased head circumference, decreased body mass index and decreased salivary cortisol at age 6–10 years (Chen et al. 2008). A Cochrane review of multiple doses of antenatal steroids published in 2007 concluded that further long-term data were required (Crowther and Harding 2007), and a review of this topic published in mid-2009 concluded that concerns about brain growth following repeated courses of antenatal corticosteroid currently warranted restriction of use to a single course (Newnham and Jobe 2009).

47.2.1.4 Incidence of RDS

Prior to the use of antenatal steroids and surfactant, the incidence of RDS in newborns in Europe was 2–3 % (Hjalmarson 1981). In the mid-1980s in the USA, the incidence was reported as 1.72 % (Becerra et al. 1992). In the modern era with widespread use of antenatal steroids and surfactant, the figures quoted are less than 1 % (Rubaltelli et al. 1998). The incidence of RDS decreases with advancing gestational age, from more than 50 % in infants born at 28 weeks gestation to around 25 % in those born at 31 weeks gestation. This fall reflects the increase in endogenous surfactant production between these ages.

47.2.1.5 Risk Factors for RDS

47.2.1.5.1 Gestation

Risk factors for RDS have been well demonstrated, with prematurity being the most important. Incidence of RDS is inversely proportional to gestational age; the majority of infants born before 28 weeks gestation will have some degree of respiratory distress. RDS remains a significant problem until around 34 weeks of gestation (Lewis et al. 1996); by 35–36 weeks gestation, incidence falls to 2 % (Rubaltelli et al. 1998). Not

only are preterm lungs less mature in terms of surfactant synthesis, but epithelial protein leak is worse in these infants, leading to increased surfactant inhibition. Preterm infants are more at risk of other factors that impact on the incidence of RDS such as asphyxia, hypoxia, cold and hypotension.

47.2.1.5.2 Maternal Factors

Infants of diabetic mothers are at higher risk of developing RDS as they have abnormal surfactant synthesis (Ojomo and Coustan 1990), and insulin delays the maturation of type 2 alveolar cells delaying surfactant production (Gross et al. 1980). Maternal hypertension and prolonged membrane rupture protect against RDS. Stress raises the fetal cortisol and induces lung maturation.

Maternal alcohol use (Ioffe and Chernick 1987), smoking (Lieberman et al. 1992) and opioid and cocaine abuse all reduce RDS in the infant. Heroin is known to mature surfactant systems, and animal models of antenatal cocaine use have shown that cocaine induces surfactant synthesis (Sosenko 1993).

Antenatal steroids protect against RDS (see section on Epidemiology of RDS).

47.2.1.5.3 Fetal Factors

Male infants are at higher risk of developing RDS and suffer a more severe course. Incidence in males is 1.7 times higher, and males are more likely to die from the condition (Farrell and Avery 1975). This gender difference appears to be related to the effects of androgens which delay the maturation of the lecithin-sphingomyelin ratio and delay production of phosphatidylcholine in surfactant (Torday 1992).

Race plays a part in risk of RDS with infants of black race relatively protected. Black infants have about a one-third lower incidence than Caucasians (Hulsey et al. 1993). This protection exists even in the most immature infants (Kavvadia et al. 1998). When looking at lecithin-sphingomyelin ratio to assess lung maturity, for the same ratio more Caucasian infants develop RDS than black infants (Richardson and Torday 1994). It is hypothesised that there may be allelic

variation in surfactant proteins causing this disparity (Rishi et al. 1992).

Growth-restricted infants are more likely to develop RDS, and the disease is more severe, compared with normal weight infants of the same gestation. Growth restriction is not as strong a risk factor as gestation, so a preterm infant of similar weight to a growth-restricted older infant is more likely to develop RDS than a growth-restricted child (Piper et al. 1996).

In multiple pregnancies the second, or higher birth order infant, is at more risk of developing RDS, as are infants born following a rapid labour.

Genetic conditions resulting in surfactant protein deficiencies are a rare cause of RDS, e.g. autosomal recessive surfactant protein B deficiency. Partial protein deficiencies and polymorphisms of parts of the proteins have also been described (Cole et al. 2000; Makri et al. 2002). A family history of a sibling with RDS increases the risk for the subsequent infant.

Thyroid activity is involved in the development of surfactant systems; hypothyroid infants with RDS have lower surfactant levels than those with normal thyroid function, although the majority of hypothyroid infants do not develop RDS (Cuestas et al. 1976; Dhanireddy et al. 1983).

47.2.1.5.4 Delivery Factors

Infants born by caesarean section (CS) are at higher risk of developing RDS. Infants born by CS after a period of time in labour have more surfactant in their airway than those born without labour (Callen et al. 1979). CS without labour is associated with more RDS and transient tachypnoea of the newborn (Annibale et al. 1995; Cohen and Carson 1985; Morrison et al. 1995). Risk of RDS following elective CS without labour continues to fall between 37 and 40 weeks of gestation.

Asphyxia results in reduced lung perfusion, and ischaemia causes capillary damage. Recovery and reperfusion cause protein leak from damaged capillaries, worsening RDS (Jefferies et al. 1984). The function of surfactant decreases with acidosis and low temperature; below 34 °C surfactant cannot spread, and therefore cold or acidotic infants are more likely to develop RDS (Gluck et al. 1972).

47.2.1.6 Stepwise Approach to Respiratory Support for RDS

Management of newborn infants who either have or are likely to develop RDS is twofold: firstly, there is the need to provide initial support for the respiratory distress, and second is the instigation of the optimal lung protective strategy to prevent development of BPD. BPD will affect up to 40 % of infants born before 29 weeks, presenting a significant healthcare burden (Patel and Greenough 2008). Every effort should be made to deliver preterm infants at high risk of RDS in centres with the appropriate skills and resources available to provide the best possible care (Sweet et al. 2007).

47.2.1.6.1 Delivery Room Management

Most very premature infants will need some form of respiratory support in the first few minutes of life. Most resuscitation guidelines are drawn up with term infants in mind and may not translate accurately to preterm infants at high risk of RDS and BPD. Until recently premature infants were routinely stabilised using 100 % oxygen; many were intubated and given surfactant as a standard procedure, regardless of their respiratory effort. We now know that 100 % oxygen is not the best choice of gas to use (Saugstad et al. 2008) and several studies are underway to determine the most appropriate initial oxygen concentration to use, as well as the best oxygen saturations to target (Castillo et al. 2008). Centile charts for normal oxygen saturations for preterm infants are now being developed (Dawson et al. 2009a). There are good theoretical, clinical and animal data for using positive end-expiratory pressure (PEEP) at delivery. Animal data have demonstrated that PEEP reduces alveolar-arterial oxygen gradient (Probyn et al. 2004), protects from lung injury (Jobe et al. 2002), preserves the surfactant pool (Michna et al. 1999), improves oxygenation and improves ventilation-perfusion matching (Schlessel et al. 1989; Finer et al. 2004). PEEP also accelerates formation of FRC (Siew et al. 2009) and protects the lungs by keeping the alveoli open (Nilsson et al. 1980). Using a resuscitation device that is able to give PEEP would seem advantageous but so far has not

shown improved outcomes in terms of saturations at 5 min or need for endotracheal intubation (Dawson et al. 2009b). Use of CPAP to treat preterm infants has been shown to reduce rates of endotracheal intubation (Lindner et al. 1999; Lundstrom 2003; Stevens et al. 2007), but the disadvantage is that any surfactant treatment is delayed. PEEP or CPAP from the delivery room onward has been shown to be as good as initial ventilation and surfactant treatment, but not any better (Morley et al. 2008), and is discussed further in the CPAP section of this chapter. CPAP and sustained inflations can be used to help the infant establish FRC (te Pas et al. 2009a; te Pas and Walther 2007). It is important to carefully control any positive pressure support given in the delivery room to avoid damaging the lungs. Animal studies have shown that even a few large volume inflations can damage newborn lungs (Bjorklund et al. 1997; Dreyfuss and Saumon 1992; Hernandez et al. 1989) and currently the majority of respiratory support systems used in the delivery room do not allow the clinician to measure the delivered volume (Schmolzer et al. 2010). In the absence of respiratory function, monitoring the initial stabilisation and transfer from the delivery room to the neonatal intensive care unit (NICU) should be guided by oxygen saturations and chest movement. However, Tracy et al. suggest that this clinically determined ventilation commonly results in hypocarbia, hyperoxia or both (Tracy et al. 2004).

47.2.1.6.2 General Management

Infants with RDS should be nursed in a thermoneutral environment, with cardiovascular and respiratory monitoring. Once initial examination is complete, infants should be handled as little as possible and nursed prone to maximise oxygenation and respiratory muscle coordination (Hand et al. 2007; Leipala et al. 2003; Wells et al. 2005). As RDS is clinically indistinguishable from sepsis, infants with ongoing respiratory symptoms should have intravenous access, blood sent for full blood count, a chest x-ray, septic markers and blood culture and should receive antibiotics.

Infants with significant increased work of breathing should not initially receive enteral

feeds, but be managed with intravenous fluid titrated against urine output and plasma sodium. Very low birth weight infants who are likely to need ongoing respiratory support require early parental nutrition for optimal lung growth and recovery. Anaemia and coagulation abnormalities need to be carefully controlled; blood pressure should be maintained with crystalloid and if necessary with inotropic support. Arterial oxygen levels should be kept between 50 and 75 mmHg (7–10 kPa); ongoing clinical trials, such as BOOST2, aim to determine the optimal oxygen saturations for this group of infants. The European Consensus Guidelines on the Management of Neonatal RDS currently recommend that oxygen saturations, in infants receiving supplemental oxygen, should be kept below 95 % (Sweet et al. 2007). Hypocarbia must be avoided due to the effect on cerebral blood flow (Garland et al. 1995). A degree of permissive hypercarbia appears safe (Miller and Carlo 2007) and is associated with lower rates of BPD (Thome and Ambalavanan 2009).

47.2.1.6.3 Supplemental Oxygen

Infants with the mildest degree of RDS may need only supplemental oxygen and good general care. Supplemental oxygen may be delivered into the isolette, given directly as subnasal oxygen or delivered via a hood or head box. With increasing disease severity, oxygen requirements climb, work of breathing increases, the infant tires, carbon dioxide (PaCO_2) levels rise and the pH falls. The infant may have desaturations or apnoeas at which point positive pressure support is required. The British Association of Perinatal Medicine (BAPM) suggests instigation of CPAP support if the inspired oxygen requirement reaches 40 %, if the pH falls below 7.25 or if the PaCO_2 rises above 50 mmHg (6.7 kPa) (British Association of Perinatal Medicine T 2005).

47.2.1.6.4 Continuous Positive Airway Pressure

CPAP was first used in neonates in 1971 (Gregory et al. 1971) and has grown hugely in popularity, particularly over the last 15 years. It has been advocated as a gentler form of respiratory support

(Jacobsen et al. 1993) and has been shown to have many physiological benefits. These include decreasing the likelihood of upper airway collapse and decreasing upper airway resistance by splinting and increasing the cross-sectional area of the pharynx (Miller et al. 1990). CPAP reduces obstructive apnoeas (Miller et al. 1985) and alters the shape of the diaphragm, improving lung compliance and decreasing lung resistance (Gaon et al. 1999). It allows larger tidal volumes for the same respiratory effort and conserves surfactant. CPAP has also been demonstrated to increase FRC (Richardson and Jung 1978; Richardson et al. 1980), stabilise the chest wall (Locke et al. 1991), improve lung volumes (Harris et al. 1976; Yu and Rolfe 1977) and improve oxygenation (Durand et al. 1983).

47.2.1.6.4.1 Generating CPAP Pressure

CPAP can be generated by a ventilator, by an underwater bubbling circuit and by variable flow drivers. There is little evidence to support one form of CPAP delivery over another, a conclusion reached by Cochrane review in 2008 (De Paoli et al. 2008). There are reports that CPAP from variable flow circuits may be superior to CPAP via a ventilator (Pandit et al. 2001; Huckstadt et al. 2003; Courtney et al. 2001) with increased tidal volume, improved thoraco-abdominal synchrony (Boumceid et al. 2007), more stable airway pressure and decreased work of breathing (Moa et al. 1988). However, other studies have not found any differences in respiratory rate, heart rate, blood pressure or comfort levels between the devices (Ahluwalia et al. 1998) nor any difference in rates of extubation failure (Stefanescu et al. 2003).

Studies that have compared ventilator generated CPAP with underwater bubbling CPAP have also seen mixed results. Animal studies showed improved airway patency, higher pH and improved oxygenation in bubble circuits compared with ventilator CPAP (Pillow et al. 2007), while another study described more stable pressure at the prong during ventilator CPAP (Kahn et al. 2007). There has been debate about whether bubble CPAP is superior to ventilator CPAP due to oscillations in the delivered pressure caused

by the bubbling (Lee et al. 1998), but it appears that vigorous bubbling is no better than gentle bubbling (Morley et al. 2005) and the oscillations are dramatically attenuated on reaching the small airways (Kahn et al. 2007). One clinical study that attempted to compare ventilator with bubble CPAP found reduced minute volume, but also reduced respiratory rates in the bubble CPAP group with no difference in blood gases (Lee et al. 1998).

Studies have also compared variable flow CPAP with bubble CPAP. One group found that bubble CPAP was not as good as variable flow CPAP at improving work of breathing and thoraco-abdominal synchrony (Liptsen et al. 2005), and another group found infants treated with bubble CPAP had higher oxygen requirements and respiratory rates (Mazzella et al. 2001). A third, more recent study determined that bubble CPAP was equally as effective as variable flow in preventing extubation failure and was more effective in infants who had been ventilated for longer (Gupta et al. 2009). Clinically important outcomes of different CPAP devices require further evaluation in randomised trials.

47.2.1.6.4.2 Nasal Interface During CPAP

CPAP was originally described using either an endotracheal tube or various head chambers and masks. These were associated with severe side effects and are no longer used. Endotracheal CPAP has been shown to increase work of breathing (Kim 1989; Davis and Henderson-Smart 2001; LeSouef et al. 1984), and CPAP is now delivered via a variety of short and long, single and bi-nasal prongs, or by nasal mask.

Long nasopharyngeal tubes, passed through one nostril to sit above the epiglottis, are still used but have high intrinsic resistance, and therefore a significant amount of the distending pressure is lost along the tube, sometimes more than 4 cm H₂O (De Paoli et al. 2002). Shorter single nasal prongs can be used but also have high resistance, and pressure is also lost via the contralateral nostril. Short bi-nasal prongs, of which there are several designs, provide a low resistance interface (De Paoli et al. 2002). Their use has been shown to prevent more re-intubations

than single nasal or nasopharyngeal prongs (relative risk (RR) 0.59, 95 % CI 0.41, 0.85, number needed to treat (NNT) was 5) (De Paoli et al. 2008). Small nasal masks have also been developed, initially in the belief that they caused less trauma. There is minimal data regarding their use, efficacy or safety, and a recent study showed that mask CPAP caused as much nasal trauma as bi-nasal prongs (Yong et al. 2005), albeit at different sites. The use of nasal masks needs to be properly investigated.

47.2.1.6.4.3 Indications for CPAP: Delivery Room and Early CPAP

In much of the developed world, management of very preterm infants in the delivery room has included endotracheal intubation and early surfactant treatment. However, a series of observational studies suggested that preterm infants managed well with initial CPAP support, reducing intubation and BPD rates, without increasing mortality or morbidity (Jacobsen et al. 1993; De Klerk and De Klerk 2001; Kamper et al. 1993; Van Marter et al. 2000). Following these publications CPAP gained more credibility as a first-line treatment and was extensively used in very low birth weight infants (Finer et al. 2004; Ammari et al. 2005). Starting CPAP soon after birth not only avoids endotracheal intubation and its inherent risks (O'Donnell et al. 2006) but also delays any surfactant treatment (Stevens et al. 2007). RCTs and meta-analyses of premature infants managed with early CPAP compared with intubation and ventilation had failed to detect differences between groups (Han et al. 1987; Sandri et al. 2004; Subramaniam et al. 2005). One study did find lower rates of BPD in infants treated with early CPAP, but the group had also received a sustained inflation at stabilisation which may have affected the results (te Pas and Walther 2007).

The COIN trial randomised infants less than 28 weeks of gestation to either CPAP or intubation in the delivery room (Morley et al. 2008). This trial found that half of the infants in the CPAP group never required intubation. CPAP-treated infants had a significantly lower rate of death or BPD at 28 days, but not at 36 weeks corrected age. CPAP-treated infants also had a

higher rate of pneumothorax, but no differences were found in any other adverse outcomes. From this large RCT, it would appear that CPAP is an acceptable alternative to intubation in the delivery room as many small babies who breathe spontaneously at birth were successfully treated without mechanical ventilation. It is possible that the higher pneumothorax rate in the CPAP group was due to surfactant deficiency. The challenge is not only to look at ways to support infants with CPAP but also to replace surfactant in a timely manner if necessary (Hascoet et al. 2008).

47.2.1.6.4.4 Indication for CPAP:

Post-extubation

As lung protective strategies have evolved, premature infants are being extubated earlier. Premature infants will have ongoing lung disease (Fox et al. 1981), poor thoraco-abdominal wall co-ordination (Locke et al. 1991) and apnoea of prematurity (Kattwinkel et al. 1975). They can develop progressive atelectasis (Finer et al. 1979) and many do not manage without ventilation for long (Annibale et al. 1994; Davis and Henderson-Smart 2000; Higgins et al. 1991). Systematic review of nine trials randomising infants to CPAP or head box oxygen post-extubation showed reduced need for additional respiratory support in the CPAP group (RR 0.62 95 % CI 0.51, 0.76, with NNT 6) (Davis and Henderson-Smart 2003). No difference was seen in terms of BPD. In these studies many infants in the head box oxygen group were successfully 'rescued' with CPAP treatment, and as a result the review found no difference in re-intubation rates. Extubation to CPAP was only advantageous if CPAP pressures were at least 5 cm H₂O. The review concluded that CPAP is beneficial post-extubation, but if resources are limited, there is no harm in restricting CPAP use after extubation to those infants who are unable to manage in head box oxygen alone. Current European guidelines recommend that preterm infants should be placed on CPAP following extubation (Sweet et al. 2007).

47.2.1.6.4.5 Optimal CPAP Pressure

Deciding optimal CPAP pressure with which to treat infants is difficult. Animal data suggests

that alveolar-arterial gradient falls with increasing PEEP, up to 8 cm H₂O (Probyn et al. 2004). Human data shows increasing FRC and tidal volume, with decreasing respiratory rate and thoraco-abdominal asynchrony, as PEEP increases from 0 to 8 cm H₂O (Elgellab et al. 2001). Laboratory data demonstrated that different prong systems result in the loss of several centimetres of water pressure across the prongs (De Paoli et al. 2002), and other studies have shown that further pressure loss occurs between the prong and the pharynx (De Paoli et al. 2005). There is much to learn about optimal CPAP pressures, and it is unlikely that any single pressure will be appropriate for the duration of an infant's illness. It would be more realistic to titrate CPAP pressure against severity of the lung disease at a given time (Davis et al. 2009).

47.2.1.6.4.6 CPAP Complications

Success of CPAP support is dependent on training and experience of both medical and nursing staff. Clinical skills in delivering CPAP support increase with time (Aly et al. 2004). The aim of CPAP is to pressurise the infants nasopharynx and lungs, but nasal prong fit is inexact and gas leak from the mouth and nose means that delivered pressure may be lower than intended (Kahn et al. 2007). Optimal prong size, position, angle and strapping all affect pressure delivery. Chin strapping may be used to reduce leak, but there is no evidence that this increases the delivered pressure. It can be difficult to achieve a therapeutic distending pressure in some infants, resulting in failure of CPAP treatment.

Gastric distension is a well-recognised side effect of CPAP although CPAP does not appear to increase the risk of necrotising enterocolitis (Aly et al. 2009) and may actually increase the speed of gastric emptying (Gounaris et al. 2004). Standard practice includes insertion of a gastric tube that is left open to air, with the aim of venting the stomach, although there is no evidence that this occurs. Nasal trauma has been reported in up to 20 % of infants receiving nasal CPAP (Robertson et al. 1996). Similar rates of injury between nasal prongs, masks and nasopharyngeal tubes have been reported (Yong et al. 2005;

Buettiker et al. 2004). Duration of CPAP support has so far been shown to be the strongest risk factor for traumatic injury (Yong et al. 2005). Early RCTs of CPAP report increased rates of pneumothoraces (Ho et al. 2002) and recent trials have shown similar rates (Morley et al. 2008; Sandri et al. 2009). Several case reports exist of more unusual complications including pneumopericardium (Turkbay et al. 2007), pulmonary interstitial emphysema (Arioni et al. 2006) and ingested nasal tubes (Duran et al. 2005). There is some data to suggest that CPAP increases infection rates, possibly secondary to trauma to the nasal mucosa (Rønnestad et al. 2005).

47.2.1.6.5 INSURE Technique

Increasing numbers of preterm infants are managed with CPAP support from birth, but concerns remain about pneumothorax rates and the delay in any surfactant treatment required. Clinicians have become interested in a technique that incorporates a brief period of intubation, to administer surfactant, followed by rapid extubation to CPAP which may overcome these problems. The technique has become known as INSURE (intubation-surfactant-extubation), and several studies have tested this method against standard ventilation techniques (Blennow et al. 1999; Bohlin et al. 2007; Thomson 2002; Verder et al. 1999).

Systematic review has shown that in infants at high risk of early RDS, early prophylactic surfactant in the first 2 h of life is better than later selective surfactant use with respect to BPD, death and air leak (Soll and Morley 2001). It has also been reported that quick intubation for surfactant delivery was most efficacious when done early (Blennow et al. 1999; Bohlin et al. 2007) with improved oxygen, less mechanical ventilation and less BPD (Thomson 2002; Verder et al. 1999; Verder 2007).

Meta-analysis of six INSURE papers (Stevens et al. 2007) has shown reduction in BPD in the INSURE group, compared with traditional treatment of surfactant and ongoing ventilation (RR 0.51 95 % CI 0.26, 0.99). The review also found that INSURE-treated infants had less need for mechanical ventilation (RR 0.67, 95 % CI 0.57, 0.79) and fewer air leaks (RR 0.52, 95 %

CI 0.28, 0.96) but had an increase in surfactant use. Stratified analysis, by oxygen requirement at study entry, found that a lower threshold of intervention, at an inspired oxygen below 45 %, resulted in lower rates of pneumothorax (RR 0.46, 95 % CI 0.23, 0.93) and less BPD (RR 0.43, 95 % CI 0.20, 0.92). Higher thresholds were associated with higher rates of patent ductus arteriosus (RR 2.15, 95 % CI 1.09, 4.13). Further studies comparing INSURE with ongoing ventilation, published since the meta-analysis, have added further weight to its findings (Rojas et al. 2009). The REVE trial also compared the INSURE technique with ongoing ventilation post-surfactant treatment, and the results suggest that the technique has most benefit for the youngest infants at 25–26 weeks gestation (Truffert et al. 2008).

The technique may not be risk-free; it still requires intubation which has inherent risks, and data suggest that INSURE results in a period of depressed brain activity (van de Berg et al. 2010). These studies have not answered the question of whether it is better to treat infants with the INSURE technique or to treat with CPAP alone and give rescue surfactant, via brief intubation, only if CPAP support is insufficient. One small Scandinavian study has addressed this question and found that the INSURE group had better oxygenation and reduced need for mechanical ventilation (Verder et al. 1994) compared with the CPAP and rescue surfactant group. The large multicentre CURPAP study also aimed to answer this question (Sandri et al. 2008), and the presented results show that there were no differences between groups in the need for mechanical ventilation, or for the combined outcome of death or BPD (Sandri et al. 2009). The implication for clinicians is that CPAP with rescue surfactant was no worse than prophylactic surfactant followed by CPAP support. There is a need to individualise initial CPAP support with early rescue surfactant based on clinical criteria. The Vermont-Oxford Network is now running a three-armed trial comparing traditional intubation, surfactant and ongoing ventilation with either INSURE or CPAP and rescue surfactant (Sinha et al. 2008).

47.2.1.6.6 High-Flow Humidified Nasal Cannula Oxygen Delivery

High-flow nasal cannulae deliver gas at 2–8 L/min into the nose, via small prongs which are loose fitting in the nostrils. The technique has evolved from subnasal oxygen treatment at low flows, less than 2 L/min, as clinicians have attempted to support more infants without using traditional CPAP. The use of humidified high-flow systems has increased rapidly over the last few years, particularly as it is felt that the system is easier to use (Shoemaker et al. 2007) and provides more patient comfort.

Traditional CPAP delivery has disadvantages using of tight-fitting head wraps, the need for careful positioning, compression of the nose and nasal trauma, and it is sometimes poorly tolerated by the infant. The use of small cannulae to generate positive pressure could reduce many of these issues; however, early equipment, developed from the original low-flow systems, were poorly heated and humidified. This limited their use due to risk of nasal mucosa injury, mucosal bleeding, thickened secretions and nosocomial infection (Kopelman and Holbert 2003; Woodhead et al. 2006). The development of heated humidified high-flow gas delivery via nasal cannulae (HHHFNC) may circumvent these issues. Such circuits are reported to decrease work of breathing and prevent re-intubation more effectively than high flow from a standard, non-heated, non-humidified nasal cannula (Woodhead et al. 2006).

Studies have shown that HHHFNC, at relatively low flows of 1–2 L/min, can generate a positive pressure in the airway of preterm infants (Sreenan et al. 2001); however, HHHFNC does not currently allow the measurement of delivered pressure, without a separate invasive process such as an oesophageal pressure probe. Some data exist suggesting that HHHFNC does not produce excessive distending pressures (Kubicka et al. 2008; Saslow et al. 2006) and that very high flows would be needed to generate significant positive pressure. Other data has demonstrated high and variable delivered pressures (Shoemaker et al. 2007; Campbell et al. 2006), and reports exist that demonstrate potentially hazardous pressures,

especially in very small infants (Sreenan et al. 2001; Quinteros et al. 2009; Chang et al. 2005).

Specific gas flow to obtain a certain delivered pressure is unknown; the pressure generated in the pharynx will depend on leak at the nose (Lampland et al. 2009), which in turn depends on the size of the patients nostril, and the presence of any secretions sealing the nares. Some algorithms exist to guide flow selection, but they depend on a consistent level of leak being present, which is not necessarily the case in practice (Wilkinson et al. 2008). If the infant's mouth is closed and the cannulae become functionally 'sealed' in the nares due to secretions or tight-fitting cannulae, then flow will continue to increase the nasopharyngeal pressure until an outlet is found. This could result in significant lung and gastrointestinal overdistention. A recent report describes development of subcutaneous scalp emphysema, pneumo-orbitis and pneumocephalus during HHHFNC use (Jasin et al. 2008). Not all HHHFNC systems contain a pressure-limiting safety valve to protect against inadvertent high pressure, but such a system should be incorporated into future designs (Lampland et al. 2009). One further concern with HHHFNC has been adequate humidification and heating of the circuit. Anecdotal reports exist of condensation in the tubing and cannulae during flows at the lower end of the range of 'high flow', resulting in water droplets coalescing to obstruct flow or enter the nares.

Initial studies with 'high-flow' systems showed disadvantages when compared with CPAP (Campbell et al. 2006); however, partial humidification and relatively low flows were used. More recent studies have found work of breathing and lung compliance were improved during HHHFNC compared with CPAP (Saslow et al. 2006); ventilator days were decreased without adverse effects such as air leak, intraventricular haemorrhage, nosocomial infection or BPD (Shoemaker et al. 2007); and frequency and severity of apnoea and bradycardia were reduced (Shoemaker et al. 2007; Woodhead et al. 2006; Sreenan et al. 2001; Holleman-Duray et al. 2007).

It is possible that the jet of gas delivered in HHHFNC may penetrate the nasal dead space

very efficiently. As the nasal compartment contributes up to 50 % of the overall respiratory resistance (Hall et al. 2002), this effect could contribute to a reduced work of breathing compared with conventional CPAP prongs. The uptake of HHHFNC by numerous neonatal units has not been accompanied by obvious changes in neonatal outcome, but the technique has not been systematically studied. The American Association of Respiratory Care 2002 Clinical Practice Guideline (Myers 2002) states that flow for nasal cannula treatment in newborn infants should not exceed 2 L/min and acknowledges that even this flow may be excessive for the extremely low birth weight infant. There is a need for high-quality RCTs to delineate the range of delivered pressure for a given flow, for all sizes of preterm infants. Until the results of these trials are available, if an infant requires CPAP, then it can more safely be delivered with a standard device (Davis et al. 2009; So et al. 1992). A multicentre, prospective, randomised comparison of CPAP compared with HHHFNC in infants greater than 1,000 g and 28 weeks gestation, from birth or following extubation, is currently underway.

47.2.1.6.7 Non-invasive Ventilation: Nasal Intermittent Positive Pressure Ventilation (NIPPV)

NIPPV includes modes of non-invasive ventilation, characterised by CPAP augmented with mechanical inflations to a set pressure. The peak (PIP) and end-expiratory pressures, inflation rate and time can all be manipulated during NIPPV. Terminology used to describe NIPPV is varied, reflecting the different inflation strategies applied through the nasal interface. Terms include synchronised nasal intermittent positive pressure ventilation (SNIPPV) (Aghai et al. 2006; Bhandari et al. 2007; Kulkarni et al. 2006; Santin et al. 2004), nasopharyngeal-synchronised intermittent mandatory ventilation (NP-SIMV) (Friedlich et al. 1999), nasal synchronised intermittent mandatory ventilation (N-SIMV) (Kiciman et al. 1998), nasal synchronised intermittent positive pressure ventilation (nSIPPV) (Moretti et al. 1999), nasal intermittent mandatory ventilation (NIMV) (Kugelman et al. 2007)

and non-invasive pressure support ventilation (NI-PSV) (Ali et al. 2007). Nasal bi-level positive airway pressure (N-BiPAP) (Migliori et al. 2005) is also used but may be more indicative of a technique using a narrow PIP-PEEP pressure difference, long inspiratory times and low rates, during which the infant continues to breathe undisturbed.

47.2.1.6.7.1 Evolution of NIPPV

NIPPV has emerged concurrently with the drive toward minimal ventilation and lung protective strategies of respiratory support. As many as half of very low birth weight infants 'fail' initial CPAP support (Finer et al. 2004; Morley et al. 2008), requiring intubation and ventilation, and around a third 'fail' extubation to CPAP (Annibale et al. 1994; Higgins et al. 1991; Davis and Henderson-Smith 2003). Efforts to manage more small infants without invasive ventilation prompted the investigation and use of NIPPV. Neonatal NIPPV uses nasal prongs or masks, with variable leak via the mouth and nose, and usually no trigger for synchronisation. A survey of neonatal units in the UK in 2006 (Owen et al. 2008) showed that 48 % of regional nurseries were using NIPPV.

The mechanism of action of NIPPV remains unclear. Hypotheses include pharyngeal dilation and increased pharyngeal pressure (Aghai et al. 2006; Santin et al. 2004; Friedlich et al. 1999; Moretti et al. 1999; Khalaf et al. 2001) increased sighs and improved respiratory drive (Lin et al. 1998), induction of Head's paradoxical reflex (Ryan et al. 1989), increased mean airway pressure (Davis et al. 2001) increased alveolar recruitment (Khalaf et al. 2001; Courtney and Barrington 2007), increased functional residual capacity (FRC) and increased tidal and minute volume (Moretti et al. 1999). It is unclear whether mechanical inflations during NIPPV are transmitted to the chest. There is some evidence that NIPPV, compared with CPAP, improves arterial oxygen, carbon dioxide, respiratory rates and oxygen saturations (Moretti et al. 1999; Migliori et al. 2005), reduces thoraco-abdominal asynchrony (Kiciman et al. 1998) and decreases work of breathing (Aghai et al. 2006; Ali et al. 2007). NIPPV may increase tidal volumes and minute

ventilation (Moretti et al. 1999), although this finding is not consistent (Aghai et al. 2006; Ali et al. 2007).

47.2.1.6.7.2 NIPPV Delivery

NIPPV may be generated by a ventilator or specialised CPAP driver and may be delivered by nasal or nasopharyngeal prongs or by nasal mask. No studies have compared efficacy of nasal interface for NIPPV delivery. Most NIPPV delivery systems do not allow the mechanical inflations to be synchronised with spontaneous inspiration. Abdominal pneumatic capsules have been used to attempt to synchronise inflations, but their efficacy during NIPPV has not been investigated.

We do not know the optimal inflation settings in terms of PIP, PEEP, inflation rate or time for NIPPV, and these values have varied widely in published studies. The 2006 UK survey noted that the settings used by clinicians were very variable (Owen et al. 2008). No studies have investigated weaning strategies for NIPPV.

47.2.1.6.7.3 Indications for NIPPV Use

Meta-analysis of three studies (Friedlich et al. 1999; Khalaf et al. 2001; Barrington et al. 2001) comparing NIPPV with CPAP following extubation found a significant risk reduction for extubation failure (RR 0.21, 95 % CI 0.1, 0.45, NNT 3) in the NIPPV group (Davis et al. 2001). Recent studies of NIPPV post-extubation have confirmed this finding (Khorana et al. 2008; Sai Sunil Kishore et al. 2009). Meta-analysis of two studies (Lin et al. 1998; Ryan et al. 1989) comparing NIPPV with CPAP for the treatment of apnoea showed no advantage of NIPPV over CPAP (Davis et al. 2001). Some studies have now investigated the use of NIPPV for the initial treatment of respiratory disease and found reduced rates of endotracheal intubation in the NIPPV groups (Kugelman et al. 2007; Bisceglia et al. 2007). There is emerging evidence that NIPPV, when compared with ventilation (Bhandari et al. 2007) or with CPAP (Kulkarni et al. 2006; Kugelman et al. 2007), has reduced rates of BPD. Retrospective review of NIPPV-treated infants, compared with ventilated infants, shows that the smallest babies had better outcomes with respect

to BPD, death and neurodevelopmental outcome at 18–22 months (Bhandari et al. 2009). A large multicentre trial of NIPPV as a first-line treatment is now taking place (Kirpalani 2007).

47.2.1.6.7.4 NIPPV Complications

Complications similar to those seen in CPAP-treated infants are the most likely to occur, including trauma, laceration (Yong et al. 2005; Shanmugananda and Rawal 2007) and sepsis (Graham et al. 2006). Historically gastrointestinal perforations (Garland et al. 1985) and head moulding (Pape et al. 1976) were reported following NIPPV, but these have not been described in recent studies. Abdominal distension has been reported in one NIPPV study (Jackson et al. 2003), but it has also been suggested that the reduced work of breathing seen during NIPPV may reduce gastrointestinal complications (Aghai et al. 2006).

47.2.1.6.7.5 Future Directions for NIPPV

There is no evidence regarding the best device, interface, settings or weaning, nor whether synchronised NIPPV is more advantageous compared with non-synchronised NIPPV. These areas warrant further investigation to delineate how NIPPV is most beneficial (Owen et al. 2007).

47.2.1.6.8 Ventilation

Neonatal endotracheal intubation and ventilation emerged in the 1960s, and although many infants survived due to this intervention (Henderson-Smith et al. 2002), it quickly became apparent that ventilation had inherent risks: ventilator-induced lung injury (Dreyfuss and Saumon 1998), infection, development of BPD (Avery et al. 1987; Heimler et al. 1988; Pandya and Kotecha 2001) and upper airway problems. While there is now considerable debate about which preterm infants need mechanical ventilation, there have also been dramatic changes in the way neonatologists are able to deliver mechanical ventilation. The British Association of Perinatal Medicine (BAPM) suggests that infants have failed CPAP support and require ventilation if they have persistent or major apnoeas with bradycardia, become acidotic below pH 7.25 or require

more than 60 % oxygen (British Association of Perinatal Medicine T 2005).

47.2.1.6.8.1 Conventional Ventilation

Early neonatal ventilation was time cycled, was pressure limited and was not synchronised with spontaneous respiratory effort (continuous mandatory ventilation (CMV), referred to as conventional ventilation). It was however demonstrated that CMV, at inflation rates similar to the infant's own respiratory rate, could result in synchronous breathing (Greenough et al. 1983, 1987).

47.2.1.6.8.2 Triggered Ventilation

Technology now allows synchronisation of mechanical inflations with spontaneous inspiration. Success of this technique relies on the triggering device being highly sensitive, with minimal time delay. Several types of trigger have been devised, using changes in airway pressure, airway flow, transthoracic impedance and abdominal movement. Different triggers may work differently under varying respiratory conditions and movements (Kassim and Greenough 2006); flow triggers have been shown to be superior to pressure triggers (Dimitriou et al. 2001). Triggered ventilatory modes, when compared with conventional CMV, show reduced rates of air leak and shorter duration of ventilation, when started during the recovery phase of RDS (Greenough et al. 2008). They also achieve improved blood gases, more stable blood pressure and reduced work of breathing (Cleary et al. 1995). Triggered modes have not been shown to be advantageous over conventional CMV in terms of intraventricular haemorrhage (IVH), BPD or mortality (Greenough et al. 2008). Some triggered ventilation modes support all spontaneous inspirations (e.g. assist control (AC), synchronised intermittent positive pressure ventilation (SIPPV) or patient-triggered ventilation (PTV)). Other modes support only a set number of inspirations (e.g. synchronised intermittent mechanical ventilation (SIMV)), determined by the clinician. Small RCTs have suggested that supporting all inflations is superior to supporting a limited number and that low numbers of supported breaths, less than 20/min, actually increase work of breathing (Roze et al. 1995).

47.2.1.6.8.3 Volume-Targeted Ventilation (VTV)

Until recently, it had not been possible to measure tidal and minute volumes in neonates, but as devices have been developed that can make these tiny measurements, volume-targeted neonatal ventilation has emerged. There is good animal and adult evidence to suggest that controlling tidal volume can reduce volutrauma, atelectotrauma and BPD in low birth weight infants (Van Marter et al. 2000). Volume-targeted ventilation allows gas exchange at lower peak inflation pressures in both the early and recovery phases of RDS (Cheema and Ahluwalia 2001). VTV shows more consistent tidal volume delivery, fewer very large breaths and less inflammatory cytokine response (Keszler 2005). Meta-analysis of volume-targeted ventilation, compared with pressure-limited ventilation, shows lower pneumothorax and IVH rates, but no definite effect on BPD or mortality rates (McCallion et al. 2005). Long-term follow-up of infants managed with VTV, compared with pressure-limited ventilation, showed no differences in mortality, respiratory illnesses or readmissions. The volume-targeted group had lower rates of inhaled steroid and bronchodilator use (Singh et al. 2009a).

47.2.1.6.8.4 Newer Modes of Conventional Ventilation

It is possible to synchronise the end of inspiration as well as the start, such that the infant is able to determine their own inspiratory time (sometimes called flow termination, e.g. pressure support ventilation, PSV, from the Dräger Babylog ventilator). Data evaluating this mode of support suggests that the technique is associated with lower rates of asynchrony (Dimitriou et al. 1998). Pressure support ventilation combined with volume-targeted ventilation has had mixed results; there appears to be reduced inflammation compared with pressure-limited ventilation (Lista et al. 2004), whereas another study found no benefit (Nafday et al. 2005). One study found infants on PSV with volume targeting required higher mean airway pressures than those managed with SIMV (Olsen et al. 2002).

Many other modes exist, such as pressure-regulated volume-controlled ventilation (PRVC from the Servo-i ventilator); this mode combines pressure and volume control. Tidal volume and maximum pressure are set, and the ventilator uses decelerating variable flow to achieve the target tidal volume. Two RCTs using PRVC in preterm infants have been published. One demonstrated reduced grade III and IV IVH in the PRVC group, compared with CMV. In a subgroup of infants less than 1,000 g, they demonstrated shorter duration of ventilation in the PRVC group (median of 11 vs. 19 days) (Piotrowski et al. 1997). The second trial found no differences when compared with SIMV (D'Angio et al. 2005).

Volume-assured pressure support ventilation (VAPS from the VIP Bird Gold ventilator) is another form of hybrid pressure and volume-controlled ventilation, where adjustment of pressure and inspiratory time occurs within each breath, to achieve the desired volume. No studies have evaluated this mode in infants with RDS.

Proportional-assist ventilation (PAV) allows even more patient control. The infant controls the timing, frequency and magnitude of inflations, and the waveform is tailored to compensate for changes in compliance and resistance. This method of support reduces work of breathing (Schulze et al. 1996) and may allow ventilation at lower mean airway pressures (Schulze et al. 1999) with less thoraco-abdominal asynchrony (Musante et al. 2001), but infants can have longer desaturations compared with PTV and require conventional back-up inflations for periods of apnoea (Schulze et al. 2007).

Neurally adjusted ventilatory assist (NAVA) uses the electrical activity of the diaphragm to control the ventilator (Sinderby et al. 1999), and electrodes are embedded onto a gastric tube positioned in the lower oesophagus. The electrical signal triggers ventilator inflation, drives inflation pressure proportional to the respiratory effort and ceases at end inspiration. One study examining seven low birth weight infants with this technique showed improved infant-ventilator interaction and lower respiratory rates during NAVA, when compared with conventional ventilation (Beck et al. 2009).

There have been many reviews of the evidence regarding respiratory management of infants with RDS published over the past decade (Sinha et al. 2008; Sweet et al. 2007; Hascoet et al. 2008; van Kaam and Rimensberger 2007; Ambalavanan and Carlo 2006; Bancalari and del Moral 2001; Claure and Bancalari 2008; Greenough and Sharma 2005; Hummler and Schulze 2009; Ramanathan 2008; Ramanathan and Sardesai 2008; Sinha and Donn 2008); however, scientific evidence does not necessarily translate into clinical practice. A survey carried out in 2006 in the UK showed that 73 % of neonatal units chose conventional non-synchronised ventilation (CMV) as the first line of support in preterm infants with RDS. Two per cent chose CPAP as first line, 2 % chose high-frequency ventilation and 5 % chose volume-targeted ventilation (Henderson-Smart et al. 2007), and only a quarter of NICUs were able to measure tidal volumes during ventilation.

47.2.1.6.9 High-Frequency Oscillatory Ventilation (HFOV)

Early animal work investigating HFOV demonstrated that there was more lung damage with the high magnitude pressure changes used in conventional ventilation than with the high mean airway pressure (MAP) used in HFOV (Hamilton et al. 1983). Animal data has shown less protein leak in RDS when using HFOV, compared with conventional ventilation (Niblett et al. 1989). Initial trials of HFOV used low lung volume strategies. This technique may be ideal for infants with established air leak syndromes, but when infants with RDS were studied, no pulmonary benefits were found with HFOV, and higher rates of IVH were seen (The HIFI Study Group 1989). Many of the infants enrolled in the early studies would not have had continuous carbon dioxide monitoring and may have had undetected hypocarbia contributing to the poor outcomes seen (The HIFI Study Group 1989; Greisen et al. 1987; Froese and Kinsella 2005). Further animal data demonstrated that optimising lung volume prolonged the effect of exogenous surfactant (Froese et al. 1993) and that when starting HFOV it was important to fully recruit the lung using a short period of higher airway pressure. A brief period of

overdistension is less damaging than the persistent atelectasis seen in the low-volume approach (Bond and Froese 1993), and the open lung technique results in more even distribution of tidal volume and less alveolar overdistension (Frerichs et al. 2003). Froese et al. suggested that how the HFOV technique is applied is more important than the choice of mechanical device generating the oscillations (Froese and Kinsella 2005).

The next wave of clinical trials used high lung volume strategies, where clinicians reduced inspired oxygen before reducing the MAP. Acute and chronic pulmonary advantages of HFOV were then seen compared with conventional ventilation (Gerstmann et al. 1996). However, the results were not reproduced in later trials where all the infants received steroids, exogenous surfactant and early CPAP after delivery (Thome et al. 1999), all of which result in a more open lung ventilation technique in both groups. Improvements in conventional ventilation, increasing PEEP, decreasing tidal volume and synchronising inflations, have meant that the advantages of HFOV have been greatly reduced (Courtney et al. 2002). Now the pulmonary benefits of lower BPD rates and shorter duration of ventilation are only seen in infants with the most severe disease, who require high oxygen requirements (>60 %) post surfactant (Courtney et al. 2002). Routine HFOV for all RDS has not been shown to be beneficial and is now often reserved for the subset of infants with severe disease. The BAPM guidelines suggest conversion to HFOV, from conventional ventilation, for infants who have failed to respond to surfactant therapy and optimisation of conventional ventilation and who still have an oxygen requirement above 60 % and peak pressures above 30 cm H₂O (British Association of Perinatal Medicine T 2005).

A Cochrane review has concluded that there is no clear evidence that prophylactic HFOV offers important advantages over conventional ventilation, in treating premature infants with RDS. There may be a small reduction in the rate of BPD, but the evidence is weak; future HFOV trials should focus on infants who are at the highest risk of BPD (Henderson-Smart et al. 2007). It is still to be determined whether a conventional

ventilation strategy that aims to minimise volutrauma and atelectotrauma by using open lung ventilation, low tidal volumes and high PEEP is any different from HFOV (van Kaam and Rimensberger 2007).

There has been one study examining the application of high-frequency oscillations via nasal prongs showing improved PaCO₂ and pH, compared with standard CPAP (Colaizy et al. 2008); further investigation of this method may be warranted.

47.2.1.6.10 High-Frequency Jet Ventilation (HFJV)

This mode of ventilation is a modification of HFOV that delivers very short inflation times of 0.02 s via a small bore injector cannula, in the frequency range of about 4–8 Hz. HFJV is not routinely used for infants with RDS. One study demonstrated that HFJV reduced rates of BPD in preterm infants, compared with conventional ventilation (Keszler et al. 1997), but a second study was stopped early due to higher rates of IVH seen in the HFJV group (Wiswell et al. 1996).

47.2.1.6.11 Extracorporeal Membrane Oxygenation (ECMO)

ECMO describes the use of modified cardiopulmonary bypass for patients with reversible lung disease, in whom maximal standard therapy has failed. It has become accepted for the treatment of several neonatal conditions, allowing time for lung healing. Catheter size and the need for systemic anticoagulation means that the technique is usually limited to infants greater than 2 kg in weight and more than 34 weeks gestation (Revenis et al. 1992). This excludes the majority of infants likely to have severe RDS. Infants at lower gestations have reduced survival (Hirschl et al. 1993) and a significantly increased risk of IVH (Hardart and Fackler 1999). IVH is four times more likely at 34 weeks gestation than at term (Neonatal ECMO Registry of the Extracorporeal Life Support Organisation 2004). Mature infants with life-threatening RDS show benefit from ECMO treatment with survival rates of more than 80 % (Bahrami and Van Meurs 2005).

47.2.1.6.12 Partial Liquid Ventilation (PLV)

PLV involves instilling perfluorocarbon into the lungs; perfluorocarbon is capable of gas transport, and during PLV the volume of liquid instilled replaces FRC. Conventional gas ventilation is applied in addition. PLV has been shown to reduce lung injury in animal models, but there is limited data in preterm infants with RDS (Ambalavanan and Carlo 2006). One non-randomised study showed a higher than expected rate of survival in infants with severe RDS, in whom conventional treatment was failing (Leach et al. 1996).

47.2.1.6.13 Weaning from Respiratory Support

Stepping down from mechanical ventilation is a topic of as much interest as escalation of support; however, there is very little research into the best practice of weaning. There is some evidence to suggest that the AC mode of ventilation is superior to SIMV modes for weaning (Dimitriou et al. 1995; Chan and Greenough 1994), as low SIMV rates can increase oxygen consumption and increase work of breathing (Roze et al. 1995). However, a survey of UK practice in 2006, more than a decade after this evidence was published, found that 73 % of neonatal units used SIMV mode for weaning infants from ventilation (Henderson-Smart et al. 2007). There have been several methods investigated to test whether an infant is ready for extubation, the key factors being an infant's respiratory drive and their lung compliance.

Use of CPAP following extubation has been shown to be superior to head box oxygen, if the CPAP pressure is at least 5 cm H₂O (Davis and Henderson-Smart 2003). In addition, use of NIPPV has been shown to prevent more extubation failures than CPAP alone (Davis et al. 2001). Weaning from NIPPV has not been studied, and weaning from CPAP has been the subject of very few studies. One study suggests decreasing CPAP support to pressures of 4–5 cm H₂O and then stopping (Singh et al. 2006); this is the alternative to 'cycling' the infant through increasing periods of time off CPAP. The 'cycling' method has not

been shown to have any significant advantages and prolongs the time the infant spends on CPAP support (Soe et al. 2006).

47.2.1.6.14 Summary of Respiratory Support

Currently the data are not conclusive to support or refute either starting with ventilation and weaning quickly or starting with minimal support and only escalating care if the infant is not managing. Ideal ventilation delivers consistent tidal and minute volumes, responds quickly to changing demands and allows the infant to breathe at the lowest pressures with the least work of breathing. Further RCTs comparing different modalities, for specific clinical conditions, are required before any single mode can be justified as being superior to another.

47.2.1.7 Rationale for Using Adjunctive Therapies During CPAP or Mechanical Ventilation for RDS

47.2.1.7.1 Exogenous Surfactant

The introduction of surfactant replacement in the late 1980s reduced mortality due to RDS but left NICUs with the burden of survivors with BPD, as survival increased, so did the rate of BPD (Hintz et al. 2005). Debate continues today about the need for surfactant administration, which surfactant to use, the most appropriate timing for surfactant delivery, the best dose and optimal mode of surfactant delivery, to treat RDS and prevent BPD. Surfactant has been shown to decrease rates of pneumothorax by 30–65 % and decrease mortality by up to 40 % (Halliday 2005).

47.2.1.7.1.1 Structure and Function of Surfactant

Surfactant is a complex system of phospholipids – mainly dipalmitoyl phosphatidylcholine, neutral lipids, proteins and glycoproteins. Surfactant is produced and assembled in type 2 pneumocytes from 22 weeks of gestation onwards, and the number of type 2 pneumocytes increases throughout gestation. Surfactant is stored in the lamellar bodies of the pneumocytes and is later extruded into the air spaces.

A healthy term infant has about ten times the pool of surfactant compared with a premature baby with RDS (Adams et al. 1970; Jackson et al. 1986).

The main effect of surfactant is reduction of surface tension; phosphatidylcholine produces a monolayer that reduces surface tension by about two-thirds. Other phospholipids, along with surfactant proteins, further reduce surface tension to almost zero (Veldhuizen et al. 1998). Surface tension is responsible for approximately two-thirds of the elastic recoil forces of the lung, so by reducing surface tension, the surfactant prevents the air spaces from collapsing at end expiration. The lowered surface tension also allows re-expansion of the terminal airways with less force. Maximum lung volumes are increased and lung expansion is more uniform. Exogenous surfactants can mimic the effects of natural surfactant, but it takes up to ten times the quantity of exogenous surfactant to generate the same effects as endogenous surfactant (Seidner et al. 1988; Ikegami et al. 1989).

47.2.1.7.1.2 Surfactant Preparations

Improved outcomes are seen with animal-derived surfactants (Soll and Blanco 2001) or surfactants containing additional proteins or peptides, rather than phospholipids alone (Moya et al. 2005). Studies have shown more improvements in FRC and compliance when using porcine-derived surfactant (poractant alfa – Curosurf™) compared with synthetic surfactant (colfosceril – Exosurf™) (Stenson et al. 1994) and when using bovine-derived surfactants beractant (Survanta™) (Cotton et al. 1993) or calfactant (Infasurf™) (Onrust et al. 1999) compared with colfosceril. Although few studies have directly compared different animal-derived surfactants, there is some data to suggest a quicker improvement in oxygenation with poractant alfa (Speer et al. 1995; Ramanathan et al. 2004). Newer artificial surfactants are now emerging which contain an artificial peptide (sinapultide) similar to surfactant protein B (lucinactant – Surfaxin™). Early data suggest that this product may be as good as animal-derived compounds (Moya et al. 2005, 2007).

47.2.1.7.1.3 Timing of First Surfactant Dose

Using surfactant prior to the onset RDS can reduce ventilator-induced lung injury (Halliday 2006; Donn and Sinha 2006). Prophylactic versus selective rescue surfactant has been shown to be superior in terms of mortality (OR 0.61 95 % CI 0.28, 0.77), BPD or death (OR 0.85 95 % CI 0.76, 0.95) and pneumothorax (OR 0.54, 95 % CI 0.42, 0.84) (Soll and Morley 2001). However, there has not been shown to be a difference in mortality depending on whether the dose is given prior to mechanical ventilation or following stabilisation (Kendig et al. 1998); there is no definite answer as to how early, early treatment should be (Soll and Morley 2001; Yost and Soll 2000). Currently data would suggest that there is not much difference between early CPAP with prophylactic surfactant via brief intubation, early CPAP and selective rescue surfactant, intubation with prophylactic surfactant or rescue endotracheal intubation and rescue surfactant (Thomson 2002).

47.2.1.7.1.4 Dose of Surfactant

The dose of surfactant recommended by most manufacturers is 100 mg/kg. Smaller doses have been shown to be less effective (Konishi et al. 1988; Halliday et al. 1993), and larger doses may have a quicker effect but confer no ongoing advantages (Halliday et al. 1993). Manufacturers recommend repeat doses at 12 h, but if there is severe disease with extensive protein leak, much of the second dose may be inactivated. Early delivery of the second dose in infants with high ventilatory or oxygen requirements may be more advantageous (Figuera-Aloy et al. 2001). A Cochrane review looking at single versus multiple doses of surfactant described two papers using animal-derived surfactants showing that multiple doses resulted in fewer pneumothoraces (RR 0.51, 95 % CI 0.30, 0.88) and a trend towards lower mortality (RR 0.63, 95 % CI 0.39, 1.02). They also described one study, using synthetic surfactant, that showed lower rates of necrotising enterocolitis (NEC) following multiple doses (RR 0.20, 95 % CI 0.08, 0.51) and lower mortality (RR 0.56, 95 % CI 0.39, 0.81). The review concluded that if an infant has ongoing respiratory

insufficiency, then repeated doses of surfactant are beneficial (Soll and Ozek 2009). Studies have found no benefit in delivery of more than two doses of surfactant (The OSIRIS Collaborative Group 1992).

47.2.1.7.1.5 Mode of Surfactant Delivery

Almost all surfactant is given directly into the endotracheal tube as a bolus. There has not been shown to be any benefit in performing physical manoeuvres aiming to direct surfactant into different areas of the lungs (Zola et al. 1993). In the modern era of minimal ventilation, there is considerable interest in a technique of surfactant delivery that does not require intubation. Endotracheal intubation has inherent risks; it frequently takes longer than the recommended time to perform (O'Donnell et al. 2006) and is often not successful at the first attempt (Leone et al. 2005). There are reports of success using alternative delivery techniques. One group has reported using surfactant delivered via a small endotracheal catheter, under direct vision, and showed that the process was well tolerated and first attempt at administration was successful in 80 % (Kribs et al. 2008). This method is now the subject of a randomised controlled trial. Two groups have published studies of aerosolised surfactant delivery, which appears feasible and safe (Berggren et al. 2000; Jorch et al. 1997) but requires further study (Mazela et al. 2007), as animal data have suggested that drug distribution in the lungs may be very variable (Lewis et al. 1991). A recent report of aerosolised lucinactant (Aerosurf™) also appears feasible and safe (Finer et al. 2006). Another group has delivered surfactant via laryngeal masks (Trevisanuto et al. 2005); this is also now the subject of an RCT. Kattwinkel et al. used surfactant instilled into the pharynx prior to delivery of the baby and reported that the method was simple and safe and warrants a randomised trial (Kattwinkel et al. 2004).

47.2.1.7.1.6 Adverse Events During Surfactant Delivery

Surfactant delivery is not without adverse effects. Infants can have transient hypoxia and bradycardia (Liechty et al. 1991) along with flattening

of the EEG (electroencephalogram) (Hellstrom-Westas et al. 1992). A recent report demonstrated that the endotracheal tube is frequently obstructed following surfactant administration and infants exhibit increased ventilatory requirements for up to an hour following surfactant delivery (Wheeler et al. 2009).

47.2.1.7.1.7 Nonresponders to Surfactant

Lack of response to surfactant treatment may indicate persistent pulmonary hypertension, patent ductus arteriosus (PDA), air leak, shock, congenital infection or asphyxia (Wirbelauer and Speer 2009). In the absence of these confounding conditions, failure of response confers a worse prognosis (Skelton and Jeffery 1996; Kuint et al. 1994).

47.2.1.7.1.8 Surfactant Conclusion

Surfactant improves outcomes for small ventilated infants, but many of the trials investigating surfactant use were done in the pre-steroid era and general anaesthetic was routinely used for caesarean sections. The results, therefore, may not be so applicable to today's population of pre-term babies. In some infants who have received antenatal steroids, who are not affected by anaesthetic agents and who are supported with early CPAP, it is not clear whether exogenous surfactant is needed at all.

47.2.1.7.2 Inhaled Nitric Oxide

Nitric oxide is a potent pulmonary vasodilator and has been shown to have profound effects on gas exchange (Gaston et al. 1994). Its use improves ventilation-perfusion mismatching, allowing improved oxygenation and reduced ventilation. Inhaled nitric oxide has been shown to be beneficial in term infants with respiratory disease, but the results are less clear, and more variable, in infants below 34 weeks gestation (Van Meurs et al. 2005; Schreiber et al. 2003; Lindwall et al. 2005). There may be some short-term benefits, but no long-term advantages have been demonstrated in premature infants (Subhedar et al. 1997). Prophylactic low dose nitric oxide in pre-term infants does not reduce the risk of developing BPD (Mercier et al. 2009). Concerns remain

regarding the effects of the drug on the developing brain and possible risk of intracranial bleeding (Van Meurs et al. 2005).

47.2.1.7.3 Antibiotics

It is impossible to differentiate between RDS and severe postnatal, or congenital, infection. Blood cultures and antibiotic treatment, with a penicillin and an aminoglycoside, for 48 h until blood cultures are shown to be negative, are standard therapy for infants with presumed RDS.

47.2.1.7.4 Methylxanthines

Methylxanthines have proven benefit in treating apnoea of prematurity. A recent large RCT has shown improved survival without neurodevelopmental disability (Schmidt et al. 2007), reduced rates of BPD and shorter duration of respiratory support (Schmidt et al. 2006a) in infants treated with caffeine. These benefits would suggest that preterm infants with RDS, who may or may not develop apnoea of prematurity, could benefit from treatment with methylxanthines.

47.2.1.7.5 Heliox

Heliox is a gas mixture in which the nitrogen has been replaced with helium. This mixture decreases pulmonary resistance and resistive work of breathing. It is hypothesised that this might improve lung function and reduce energy expenditure in infants with severe lung disease. Early observational data show that mechanical ventilation with heliox mixture does reduce resistive work of breathing and ventilatory requirements, as well as improving gas exchange in ventilated preterm infants (Migliori et al. 2009). Other reports suggest it may be useful in the treatment of pulmonary interstitial emphysema (Phatak et al. 2008). Heliox treatment, combined with CPAP, for extremely low birth weight infants is currently being studied as part of a randomised trial.

47.2.1.7.6 Diuretics

Furosemide (furosemide) increases resorption of lung fluid and produces short-term improvements in lung function. However, the early use of

diuretics in preterm infants can increase the risk of patent ductus arteriosus as frusemide stimulates production of prostaglandin E2. Repeated use of diuretics in premature infants increases the risk of ototoxicity and aminoglycoside ototoxicity (Hey Ee 2003), as well as the possibility of inducing hypovolaemia and low systemic blood pressure. Systematic review of diuretics for RDS shows no benefit on mortality, BPD, duration of mechanical ventilation, duration of oxygen treatment or length of hospital stay (Brion and Soll 2001). The trials included in the Cochrane review were completed before generalised use of antenatal steroids or surfactant replacement, but to date there is no evidence in favour of routine use of diuretic treatment in RDS (Wiswell et al. 2007). The use of diuretics should be reserved for oliguric infants with fluid retention and deteriorating lung function.

47.2.1.7.7 Analgesia, Sedation and Neuromuscular Paralysis

Opioids have regularly been used to provide analgesia and sedation for ventilated infants with RDS. Recent systematic review found no significant benefits in terms of mortality, duration of mechanical ventilation or neurodevelopmental outcomes to warrant routine use of opioids in this population (Bellu et al. 2005). Adverse effects of morphine, such as delaying achievement of full enteral feeds, need to be considered when considering opioid treatment (Menon et al. 2008). Midazolam is also commonly used for sedation of ventilated newborns, but again systematic review found no advantages when compared with either placebo or morphine. Midazolam use increased rates of adverse events including hypotension, death, longer duration of hospital stay, and more IVH and periventricular leukomalacia. The authors concluded that routine use of midazolam for sedation should not be recommended (Ng et al. 2003). Neuromuscular paralyzing agents are sometimes used to abolish spontaneous breathing patterns in infants with asynchronous respiratory effort. Cochrane review has shown that agents such as pancuronium have the potential to decrease air leak and IVH in such

infants. Uncertainty regarding the long-term pulmonary and neurological effects of paralyzing agents means that routine usage is not currently recommended (Cools and Offringa 2005).

Numerous pharmacologic agents have been used to treat infants with BPD; these are further discussed in Sect. 32.1.4, 32.1.7, and 48.1.3 of this book.

47.2.1.8 Classical Complications of RDS

The single most important complication of RDS, in terms of morbidity, treatment and cost, is bronchopulmonary dysplasia (BPD). BPD can occur even in the presence of only mild respiratory disease (Bancalari and del Moral 2001) and will affect up to 40 % of infants born before 29 weeks gestation (Patel and Greenough 2008). The use of antenatal steroids, surfactant and newer ventilatory techniques has not significantly reduced the incidence of BPD (Van Marter et al. 2001; Lemons et al. 2001).

Air leak syndromes including pulmonary interstitial emphysema, pneumothorax and pneumomediastinum used to be high in infants with RDS, but following the introduction of exogenous surfactant, the use of triggered ventilation techniques and shorter inflation times, these complication rates have fallen to about 5 % in infants ventilated for RDS (Rennie 2005).

Other major complications include PDA, intraventricular haemorrhage and renal failure. The incidence of symptomatic PDA increases with the fluid overload seen in infants with RDS (Bell et al. 1980); this in turn increases the risk of significant pulmonary haemorrhage. There has been considerable debate in the literature regarding the use of prophylactic indomethacin for very low birth weight babies with RDS, as indomethacin has been shown to reduce PDA and possibly reduce severe IVH (Fowle 1996; Fowle and Davis 2003). Long-term follow-up of infants who received prophylactic indomethacin has not demonstrated any beneficial effect on mortality or neurodevelopment (Fowle and Davis 2003). Infants with RDS require close control of PaCO₂, blood pressure and coagulation, to

minimise the risk of developing IVH and acute tubular necrosis.

47.2.1.9 Short- and Long-Term Outcome of RDS

Long-term complications following RDS may develop as a result of oxygen toxicity, ventilator-induced lung and airway injuries, or from periods of hypoxia. The major complication of RDS remains chronic lung disease, bronchopulmonary dysplasia (BPD).

47.2.1.9.1 Survival

Overall mortality from RDS is between 5 and 10 % and is rare in infants of birth weight greater than 1,500 g (Rennie 2005). Death from RDS occurs most frequently between days 2 and 7 of life. Infants who receive prolonged ventilation from birth have lower survival rates and higher rates of impairment (Gaillard et al. 2001; Walsh et al. 2005).

47.2.1.9.2 Bronchopulmonary Dysplasia: Chronic Lung Disease

The definition of BPD has evolved over recent years from the original description of oxygen dependency at 28 days with corresponding x-ray changes (Northway et al. 1967). It has now been shown that oxygen dependence at 36 weeks corrected gestational age correlates better with long-term morbidity (Shennan et al. 1988). Infants born below 32 weeks gestation are assessed at 36 weeks corrected age, or at hospital discharge, whichever is sooner, and BPD is classified as mild, moderate or severe. Infants who need supplemental oxygen at 28 days of age, but who are in air at 36 weeks corrected age, have mild disease. Infants requiring up to 30 % oxygen at 36 weeks corrected age have moderate disease, and infants requiring more than 30 % oxygen, or positive pressure support, have severe disease. Infants born after 32 weeks gestational age are assessed by the same criteria at 56 days of age, or at hospital discharge, whichever is sooner (Jobe and Bancalari 2001).

It is difficult to predict infants who will go on to develop BPD from the appearance of

the initial x-rays as the findings depend upon the amount of fetal lung fluid present and the phase of respiratory cycle in which the x-ray was taken. Positive pressure support and early surfactant use improve the x-ray appearance so early images are a poor guide to outcome (Kanto et al. 1978). The incidence of BPD in very low birth weight infants ranges from 15 to 50 %; quoted incidence varies as the proportion of extremely low birth weight babies in different studies varies (Sinha and Donn 2006). The oxygen saturation target, and ventilation strategy of individual neonatal units, influences the number of infants receiving supplemental oxygen and therefore the quoted rates of BPD. Numbers of infants with BPD have increased over recent years, and this may reflect the increased survival of very low birth weight infants. Many factors affect the risk of developing BPD: the degree of prematurity, the severity of the disease, oxygen toxicity, effects of ventilator-induced lung injury (barotrauma, volutrauma, atelectasis, shear trauma and biotrauma), PDA and the presence or absence of air leak. Infants who develop BPD commonly have exacerbations of their lung disease in childhood, requiring readmission to paediatric wards both in the first year (Mutch et al. 1986) and throughout childhood (McCormick et al. 1993). These infants are at risk of serious decompensation should they contract bronchiolitis, and regimens exist for respiratory syncytial virus prophylaxis to specific groups of children with BPD.

47.2.1.9.3 Neurological Outcome

Although most infants with RDS have normal neurological outcomes, those who require prolonged ventilation and develop BPD have more neurological sequelae than those with mild disease not requiring ventilation (Anderson and Doyle 2006). One follow-up study showed that infants with RDS who required prolonged continuous ventilation, for at least 28 days, were more likely to die or have abnormal neurological outcome, than those requiring less ventilation. The study also showed that very low birth weight infants with major cranial ultrasound

abnormalities who had prolonged ventilation, all either died or had abnormal neurodevelopmental outcome (Thomas et al. 2003).

47.2.1.10 Conclusions

RDS remains a major problem for extremely low birth weight infants. How these infants are managed in the first few minutes of life may determine their long-term outcome. BPD is a major cause of severe neonatal morbidity (Ehrenkranz et al. 2005) and mechanical ventilation is a prime risk factor (Jobe and Bancalari 2001). How to use CPAP and surfactant to the infant's best advantage, while avoiding lung injury, still needs to be determined. Optimal devices and settings for CPAP and NIPPV delivery need to be researched. On the horizon are developments such as nebulised surfactant, non-invasive ventilation, high-flow nasal cannula treatment, interactive modes of mechanical ventilation and the use of heliox. These treatments have the potential for improved management and outcome in the population of preterm infants at highest risk of RDS and are all the subject of ongoing trials.

- Use of PEEP at delivery, judicious use of supplemental oxygen, early CPAP with or without prophylactic surfactant and restriction of invasive mechanical ventilation all play a role in reducing the risk of developing BPD.
- BPD will affect up to 40 % of infants born before 29 weeks. Newer ventilatory techniques have not significantly reduced the incidence of BPD.
- Numbers of infants with BPD have increased over recent years, and this may reflect the increased survival of very low birth weight infants with RDS.
- Further research is required to define the optimal modes of respiratory support in RDS, to avoid lung injury.

47.2.2 Neonatal Pneumonia

Peter G. Davis and Louise S. Owen

Essentials to Remember

- Respiratory distress syndrome (RDS) is the most common reason for admission to a neonatal intensive care unit.
- In RDS the lungs are non-compliant and atelectatic with high surface tension and small airways collapse.
- On CXR diffuse infiltrates have the appearance of ground glass which outlines larger air-filled bronchioles.
- Risk of developing RDS varies with lung maturity which is related to gestational age and the use of antenatal steroids.
- Mortality from RDS is 5–10 %, and antenatal steroids and surfactant replacement reduce mortality rates.
- Management of RDS involves supporting respiration using a minimally invasive lung protective strategy, to reduce the risk of developing BPD.

Educational Aims

- To define neonatal pneumonia and its classification
- To describe the histopathology and common causative organisms
- To outline why neonates are susceptible to pneumonia and define subgroups at highest risk
- To describe appropriate therapy including antibiotics and respiratory support
- To describe outcomes following neonatal pneumonia

Pneumonia may be defined as inflammation of the lung with consolidation. The term is usually used to indicate infection of the lung parenchyma resulting in obliteration of alveolar air spaces by purulent exudate. The lungs are a common site of infection in the newborn. Infection may be viral or bacterial in origin and may be acquired before birth, during delivery or in the early postnatal

period. The clinical manifestations are often subtle and non-specific. Systemic signs may precede signs of respiratory distress and x-rays and blood tests have limited predictive value. It is important, therefore, to consider the diagnosis and treat early, as pneumonia is an important cause of mortality and morbidity in this age group.

47.2.2.1 Pathophysiology

47.2.2.1.1 Host Defences of the Newborn

The host defences in the lung of the newborn infant are less well developed than those of older children and adults. Polymorphonuclear neutrophils have reduced phagocytic and microbicidal activities as well as diminished capacity for chemotaxis and adhesion (Hill 1987). Natural killer cells, while normal in number, have reduced cytolytic activity against target cells. Circulating complement levels are reduced to around 50 % of levels seen in older children. Transmission of maternal IgG antibodies across the placenta confers a degree of immune protection. However, the neonate is poorly protected against organisms that predominantly evoke IgA or IgM antibodies. Importantly, preterm infants miss out on the placental transfer of antibodies which mostly occurs late in the third trimester of pregnancy.

As a result of impaired host defences, infections are more common and cause greater disruption of normal lung structure and function in both term and preterm neonates.

47.2.2.1.2 Pathology

Bacterial infections commonly give rise to inflammation of the pleura, infiltration and destruction of the bronchopulmonary tissue and exudate containing leukocytes and fibrin within the alveoli and small airways (Davies and Aherne 1962). An interstitial pattern with infiltration of mononuclear cells and lymphocytes is more typically seen in viral pneumonia.

Damage to the lungs occurs due to direct injury by the invading microorganisms and indirectly as a result of inappropriate or excessive responses by the host defence system. Direct injury is mediated by microbial enzymes, proteins and toxins that disrupt host cell membranes and metabolism. For example, group B streptococcal

(GBS) pneumonia is characterised by exudative pulmonary oedema and alveolar haemorrhage. The organism appears to injure lung microvascular endothelial cells via a pore-forming hemolysin (Gibson et al. 1999). Inflammation attracts phagocytes which release substances that may help defend the body against the invading organisms but may result in poorly regulated cascades which damage host tissues.

Injury leads to an increased airway smooth muscle tone, mucous secretion and debris within the airways. In turn, this causes increased airway resistance, partial or total airway obstruction and atelectasis or air trapping. Surfactant inactivation by proteinaceous exudate exacerbates the impairment of lung function. Gas exchange is impaired by increased barriers to alveolar diffusion, intrapulmonary shunting and ventilation-perfusion mismatch. An increased metabolic demand of the lungs and other tissues to which the infection may have spread exacerbates these problems.

Some bacterial infections are associated with typical pathological features. *Staphylococcus aureus* and *Klebsiella pneumoniae* cause extensive tissue damage and may lead to abscess formation and empyema.

47.2.2.2 Lung Mechanics

Neonatal pneumonia causes impaired lung mechanics through a variety of pathways. Respiratory drive is frequently reduced, leading to retention of carbon dioxide and culminating in apnoeic episodes requiring respiratory support. Hypoxaemia from hypoventilation is relatively easily overcome by increasing the inspired oxygen concentration.

Inflammation and infection involving the distal air spaces decreases ventilation to the affected areas. If perfusion of these areas is maintained, ventilation-perfusion mismatch occurs. When alveoli are completely filled with exudate, there may be no ventilation and extreme ventilation-perfusion inequality results. Hypoxaemia is the consequence of such an intrapulmonary shunt, and the low PaO₂ is not overcome by administering high oxygen concentrations.

Pneumonia causes leakage of proteins from the intravascular and interstitial spaces into the

alveoli. Fibrin, fibrinogen and albumin inhibit surfactant function, leading to a further reduction in functional residual capacity, decreased pulmonary compliance and increased work of breathing.

47.2.2.3 Epidemiology

47.2.2.3.1 Early Onset Pneumonia

Early onset pneumonia presents within the first 3 days of life. Transplacentally acquired pneumonia is a relatively rare form of early onset pneumonia. It includes those pneumonias caused by rubella virus, cytomegalovirus, *Treponema pallidum* and *Listeria monocytogenes*. Many of these infants are stillborn or die in the first days of life.

More commonly it is due to aspiration of infected amniotic fluid before or at the time of delivery. In developed countries, group B streptococcus (GBS) is the most common bacterial pathogen, but gram-negative organisms such as *E. coli* are also prevalent. In contrast, *E. coli* is the main organism in developing countries. Blood cultures are frequently positive when these organisms are involved. *Listeria* species, herpes simplex virus, candida, enterovirus and adenovirus have also been reported.

Initial treatment with a penicillin (penicillin G or ampicillin) and an aminoglycoside (gentamicin) is appropriate pending blood cultures. Acyclovir should be started if herpes simplex virus pneumonia is suspected. As the clinical and radiological signs of pneumonia are not specific, treatment of all cases of respiratory distress with appropriate antibiotics is the safest option.

47.2.2.3.2 Late-Onset Pneumonia

Late-onset pneumonia, beyond the first 72 h of life, may be caused by the same organisms, but *Staphylococcus aureus*, coagulase-negative Staphylococci and gram-negative bacilli are most common. Blood cultures are frequently negative in late-onset pneumonia.

Choice of antibiotics is governed by the resistance profiles of the setting. Where drug-resistant staphylococci are prevalent, the combination of vancomycin and gentamicin provides suitable cover.

47.2.2.3.3 Factors Associated with Increased Risk

Race and economic factors are associated with risk of early neonatal pneumonia. A study conducted in the 1960s showed that black infants who died in the first 48 h of life had an incidence of pneumonia of 27.7 %, compared with 11.3 % of white infants. The difference was consistent across all weight groups (Fujikura and Froehlich 1967). Similar differences were found by Naeye et al. in a series of consecutive autopsies of newborn and stillborn infants. Black infants had significantly higher rates of pneumonia (37 %) than Puerto Rican (22 %) or white infants (20 %). They also found that babies from families with the lowest income had significantly higher rates of pneumonia than infants from higher income families (Naeye et al. 1971).

Late-onset bacterial pneumonia may occur in nursery epidemics as a result of an infected health care worker or contaminated equipment. Viral epidemics have also been reported. Respiratory syncytial virus and influenza virus are amongst the causative organisms, and direct contact and droplets are the most common modes of spread.

47.2.2.4 Incidence

The reported rates of neonatal pneumonia vary widely depending on site, definition and method of ascertainment. However, it is well established that pneumonia is an important cause of mortality and morbidity in developing countries (Duke 2005). Between 750,000 and 1.2 million neonatal deaths are thought to be due to pneumonia which equates to 10 % of global child mortality (Nissen 2007). A field study in rural India found a mortality rates for pneumonia in the first month of life of 29 per 1,000 live births (Bang et al. 1993). The incidence is much lower in developed countries. Webber et al. prospectively studied neonatal pneumonia in single tertiary unit in Oxford (Webber et al. 1990). Over a 41-month period, they diagnosed 35 cases of early onset pneumonia amongst 19,569 live-born infants (1.79 per 1,000). Group B streptococcus was the predominant organism (69 %). Late-onset pneumonia occurred in 39 infants, the overwhelming majority of whom were preterm (92 %) and ventilated

(87 %). Sinha et al. conducted a retrospective cohort study of neonatal infections using data from a large health maintenance organisation. In this US setting although infection was common during the first 30 days of life, pneumonia was uncommon compared to other infections. They reported rates of pneumonia of 4 per 1,000 during a nursery stay, 0.3 per 1,000 at paediatric office visits and 0.1 per 1,000 at emergency department visits (Sinha et al. 2003).

47.2.2.5 Risk Factors

47.2.2.5.1 Early Onset Pneumonia

Ascending infection from the maternal genital tract is the most common mode of acquisition of early onset pneumonia. Therefore, prolonged rupture of the membranes, variously defined as beyond 18 or 24 h duration, is an important risk factor for neonatal pneumonia. Signs of maternal infection, e.g. maternal fever and uterine tenderness, may give early warning of an infant at risk. Frequent pelvic examinations during labour are also considered a risk factor. Persistent fetal tachycardia is a relatively specific sign of infection, and its presence on CTG during labour should be communicated to those responsible for postnatal care of the infant.

Vaginal and rectal carriage of GBS occurs in 10–20 % of pregnant women. Infants at highest risk for GBS are those whose mothers carry the organism but have little or no circulating anti-GBS immunoglobulin. Approximately 1 % of infants born to carrier mothers become infected. Early onset GBS disease affects 1.8 per 1,000 live births.

Infected dairy products are considered the most important reservoir for transmission of *Listeria monocytogenes*. Women with HIV are more susceptible to infection with this organism.

47.2.2.5.2 Late-Onset Pneumonia

Late-onset pneumonia is strongly associated with assisted ventilation, and the risk is substantially higher for preterm infants. Rates vary according to the stringency of definition. Colonisation of the endotracheal tube is common, but using strict criteria, including positive blood culture of a respiratory pathogen, the rate of late-onset pneumonia

in infants ventilated for more than 24 h in the Oxford study was 10 % (Webber et al. 1990). In a single-centre cohort study of ventilated infants of birth weight <2,000 g in St. Louis, the overall rate of ventilator-associated pneumonia was 11 %. Diagnosis was based on focal infiltrates on chest x-ray in combination with antibiotic usage for 1 week. The rate was substantially higher (28 %) in infants <28 weeks gestation (Apisarnthanarak et al. 2003). Using a less strict definition, Halliday et al. reported a pneumonia rate of 35 % in pre-term infants ventilated during a randomised trial of surfactant therapy (Halliday et al. 1984). Other risk factors for late-onset pneumonia include neurological impairments leading to aspiration and congenital abnormalities of the lung and airways, e.g. tracheo-oesophageal fistula and cystic adenomatoid malformations. Preventable factors such as poor hand washing (Harbarth et al. 1999) are important in both developed and developing countries.

47.2.2.6 Stepwise Approach to Respiratory Support

47.2.2.6.1 Basic Principles

Successful treatment of neonatal pneumonia depends on consideration of the diagnosis in the differential diagnosis of any unwell newborn infant and early commencement of appropriate antibiotic therapy. The goals of treatment are to eradicate the infection and provide adequate respiratory support to allow intact survival of the infant.

There is less evidence to guide clinicians regarding the ventilation of infants with pneumonia compared with RDS. However, the hierarchy of respiratory support is similar to that for RDS. Requirements should be titrated against an infant's needs. Regular clinical assessment, in addition to continuous cardiorespiratory and oxygen saturation monitoring, allows the clinician to gauge the infant's progress and intervene appropriately.

47.2.2.6.2 Non-invasive Support

Active infants with respiratory distress whose breathing is regular may only require supplemental oxygen to maintain normal oxygen

saturations. Additional support may be required to manage an infant with inadequate respiratory drive or severe lung disease. Sepsis in general and pneumonia in particular are often associated with apnoeic pauses. These occur in term infants but are more common in preterm infants. If apnoeic infants require frequent stimulation, i.e. more often than once per hour, or bag and mask ventilation, then additional support is required. Nasal CPAP may be useful as it reduces the work of breathing and leads to more regular respirations.

47.2.2.6.3 Invasive Support

Infants with severe respiratory distress, particularly when associated with respiratory acidosis, require intubation and ventilation. Regular assessment of blood gases is essential to avoid the dangers of excessive ventilation, i.e. hypocarbia and volutrauma as well as underventilation and worsening respiratory acidosis.

47.2.2.6.3.1 PEEP and Tidal Volume

There are no randomised trials comparing different modes of ventilation for infants with pneumonia. Given the paucity of human data, some animal data may usefully inform clinical practice. Using an adult rat model of pseudomonas pneumonia, Lin et al. showed that the choice of ventilator parameters is potentially important in determining the outcome of pneumonia (Lin et al. 2003). They compared an injurious mode of ventilation, zero PEEP and high tidal volumes with a lung protective strategy, standard PEEP and moderate tidal volume. Rats undergoing the injurious strategy had increased rates of bacteraemia and higher serum levels of inflammatory cytokines. In a series of experiments using a newborn piglet model of group B streptococcal pneumonia, van Kaam and Lachmann demonstrated the importance of PEEP and atelectasis. The use of (1) surfactant prophylaxis and (2) a strategy of peak and end-expiratory pressures designed to avoid atelectasis each independently resulted in attenuated bacterial growth and translocation into the blood stream (van Kaam et al. 2004). In a similar

study, this group compared three different PEEP levels after surfactant lavage and group B streptococcus inoculation. The lowest PEEP group had the worst lung function and the highest mortality. The highest PEEP group had higher rates of translocation of bacteria into the bloodstream than the optimum PEEP group (Lachmann et al. 2007). The implications for clinicians are that care should be exercised in choice of ventilator settings and overdistension and atelectasis should be avoided.

47.2.2.6.3.2 High-Frequency Oscillatory Ventilation and Nitric Oxide

There are no trials which definitively identify the role of high-frequency oscillatory ventilation in the management of neonatal pneumonia. Typically this form of support is reserved for the sickest infants, i.e. those with the most difficulties with oxygenation and carbon dioxide retention. Donn and Sinha appropriately caution clinicians using high-frequency ventilation for infants with sepsis as this modality may exacerbate an already compromised cardiac output (Donn and Sinha 2003). Judicious use of volume replacement and inotropes may be required when this form of ventilation is used in infants with severe respiratory failure and hemodynamic compromise. When pulmonary hypertension is a feature, typically in group B streptococcal pneumonia, the combination of high-frequency ventilation and nitric oxide may be appropriate. Kinsella and Abman suggest that for pulmonary hypertension where diffuse parenchymal disease and underinflation are features, e.g. neonatal pneumonia, recruitment of air spaces using high-frequency oscillatory ventilation enhances delivery and effectiveness of inhaled nitric oxide (Kinsella and Abman 1998).

47.2.2.6.3.3 Exogenous Surfactant Therapy

Natural surfactants contain host defence factors. Surfactant proteins A and D modulate the inflammatory response to infection and assist in phagocytosis and killing of invading organisms (Jobe 2000). Herting et al. showed that

exogenous surfactant reduced bacterial growth and improved lung compliance in a rabbit model of GBS pneumonia (Herting et al. 1997). In a retrospective study of 118 infants with culture proven GBS pneumonia, Herting et al. showed that surfactant therapy improved gas exchange in about 75 % of infants. The response was slower and smaller in magnitude than that of infants with hyaline membrane disease. In the absence of randomised trials on the topic, surfactant therapy for neonatal pneumonia may be considered a *potentially* useful therapy for infants requiring endotracheal intubation and ventilation.

47.2.2.7 Short- and Long-Term Outcomes

Duke reported case fatality rates for neonatal pneumonia of between 8 and 48 % in a variety of community- and hospital-based studies (Duke 2005). The highest rates were seen in early onset disease. The studies predominantly were from India, the exception being the Oxford study of Webber et al. which reported a mortality rate of 14 % (Webber et al. 1990). Duke noted the risk factors for death included the presence of hypoxaemia, low birth weight and absence of tachypnoea (Duke 2005).

In developed countries outcomes are generally good. However, increased mortality is associated with preterm birth, pre-existing chronic lung disease or immune deficiencies. Residual pulmonary anomalies including pneumato-coele are relatively common, particularly with staphylococcal pneumonia. These sequelae are also seen in association with *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Haemophilus influenzae* and may persist for many months. However, long-term prognosis for complete recovery is excellent (Huxtable et al. 1964).

47.2.2.8 Conclusions

Worldwide, neonatal pneumonia is an important cause of morbidity and mortality. The symptoms and signs are non-specific; therefore, the diagnosis should be suspected in any infant with

respiratory distress. Infants treated early with appropriate antibiotics have a good prognosis. Respiratory support should be matched to the infant's requirements, aiming to allow treatment and resolution of the infection without causing additional ventilator-induced damage.

Essentials to Remember

- Neonates are susceptible to pneumonia because many of the components of the host defence system are not fully developed.
- Infections can be of early onset (first 3 days of life) or late (beyond the first 3 days).
- Early infections are most commonly due to group B streptococcus and gram-negative bacteria. Initial treatment with a penicillin and an aminoglycoside is appropriate.
- Late infections are most commonly due to staphylococci and gram-negative bacilli. Antibiotic therapy should be guided by local resistance patterns; where resistant staphylococci are prevalent, vancomycin and an aminoglycoside provide suitable cover.
- Prolonged rupture of membranes, signs of maternal infection and persistent fetal tachycardia may provide early warning of the risk of early onset pneumonia.
- The combination of assisted ventilation and prematurity increases the risk of late-onset infection.
- The level of respiratory support should be titrated against the infant's requirements: supplemental oxygen, nasal CPAP and conventional and high-frequency ventilation via an endotracheal tube may be required.
- Outcomes following neonatal pneumonia in developed countries are generally good. Risks of death increase with associated disorders and prematurity.

47.2.3 Meconium Aspiration Syndrome

Peter A. Dargaville

Educational Aims

This chapter aims to give an understanding of:

- The pathophysiology of MAS, in particular the causes of hypoxaemia and poor lung compliance
- The epidemiology of the condition
- The conventional and alternative means of respiratory support for MAS, including a stepwise approach to respiratory support, and the rationale for use of adjunctive therapies
- The complications and outcome of MAS

47.2.3.1 Introduction

Meconium aspiration syndrome (MAS) is a complex respiratory disease of the term and near-term neonate that continues to place a considerable burden on neonatal intensive care resources worldwide. MAS is a disease in evolution, with both the incidence and severity directly linked to improvements in antenatal and peripartum care. In the developed world, largely as a result of a more aggressive management of post-maturity, fetal growth restriction, placental dysfunction and intrapartum fetal distress, MAS has become uncommon but will never be eradicated completely. The outcome for afflicted infants has also improved substantially. In newly industrialised and developing countries, MAS remains a prominent cause of neonatal respiratory failure in the term infant, with a high risk of mortality.

MAS has features that make it stand alone amongst neonatal respiratory diseases – the unique combination of atelectasis, airflow obstruction and lung inflammation, the high risk of coexistent pulmonary hypertension and the fact of these occurring in a term infant with a mature lung structurally and biochemically. For all these reasons, management of MAS, and in

particular the ventilatory management of MAS, has been a difficult challenge for neonatologists down the years.

In this chapter, MAS is defined as respiratory distress occurring soon after delivery in a meconium-stained infant that is not otherwise explicable and is associated with a typical radiographic appearance (Wiswell and Henley 1992).

47.2.3.2 Pathophysiology

Lung dysfunction in MAS is a variable interplay of several pathophysiological disturbances, chief amongst which are airway obstruction, epithelial injury, alveolar oedema, surfactant inhibition and pulmonary hypertension. Figure 47.1 shows a schematic of the pathogenesis of MAS, indicating the antecedents to these events, the critical one being entry of meconium into the lung (Dargaville and Mills 2005).

Meconium is the viscid pigmented secretion of the fetal intestinal tract, which accumulates in the colon and distal small intestine in a layered fashion from the 12th week of fetal gestation. It is a noxious substance when inhaled, producing one of the worst forms of aspiration pneumonitis encountered in humans. Meconium has many adverse biophysical properties, including high tenacity (stickiness) (Rubin et al. 1996), extremely high surface tension (215 mN/m) (Rubin et al. 1996) and potent inhibition of surfactant function (Moses et al. 1991; Sun et al. 1993; Herting et al. 2001). Meconium is also directly toxic to the pulmonary epithelium, causing haemorrhagic alveolitis, and is chemotactic to neutrophils, activates complement and is possibly vasoactive (Oelberg et al. 1990; Dargaville et al. 2001; de Beaufort et al. 1998; Castellheim et al. 2005; Holcberg et al. 1999). These adverse properties of meconium are reflected in the sequence of pathophysiological disturbances known to occur in MAS (Fig. 47.1).

The pathogenesis of MAS after aspiration of meconium has been studied in animals with naturally occurring MAS (Shaffer et al. 1984), animal models of MAS induced using human meconium (Castellheim et al. 2005; Tyler et al. 1978; Tran et al. 1980; Davey et al. 1993; Wiswell et al. 1994; Gooding et al. 1971; Jones et al. 1996;

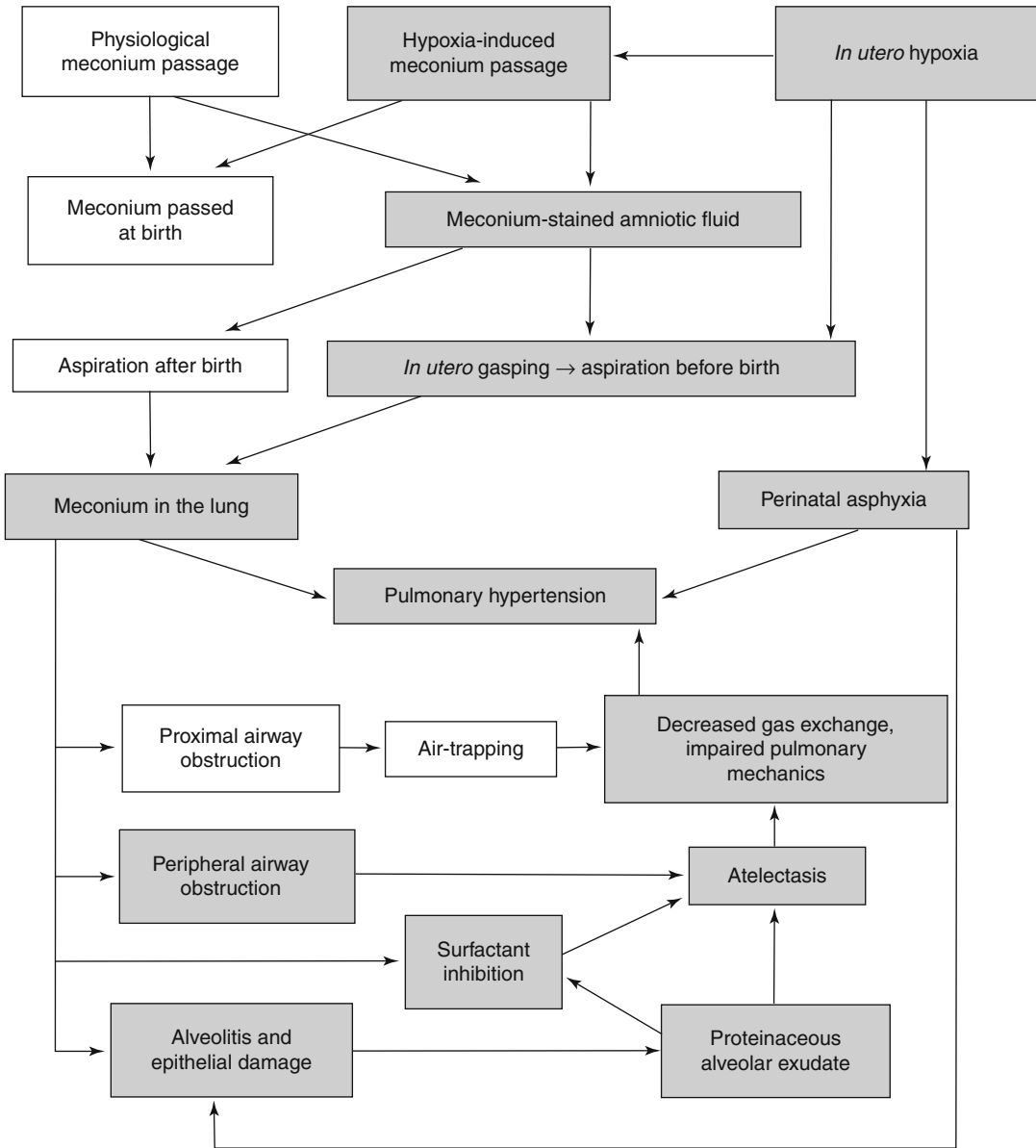
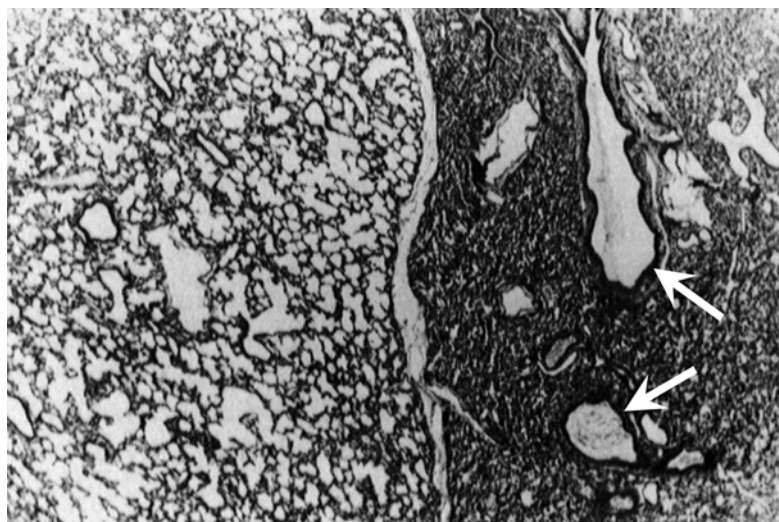


Fig. 47.1 Pathogenesis of meconium aspiration syndrome. Shaded boxes denote usual elements, and no shading denotes occasional elements (From Dargaville and Mills (2005); with permission)

Cayabyab et al. 2007) and in human infants with the disease (Dargaville et al. 2001; Dimitriou and Greenough 1995; Yeh et al. 1982). Once inhaled, meconium migrates distally down the tracheo-bronchial tree, obstructing airways of progressively smaller diameter (Tyler et al. 1978; Tran et al. 1980; Davey et al. 1993). In some instances there appears to be a considerable component of

‘ball-valve’ obstruction, with high resistance to airflow in expiration, and thus resultant gas trapping distal to the obstruction (Tran et al. 1980). If global in distribution, high functional residual capacity may result, although only in a small proportion of infants with MAS is there measurably high FRC (Dimitriou and Greenough 1995; Yeh et al. 1982), and even then only transiently

Fig. 47.2 Histological appearance of MAS. Section of lung from a piglet with experimental MAS, showing an area of normal lung expansion on the left, side by side with an area of atelectasis on the right. Meconium plugs are identified in the bronchi within the atelectatic region (arrows) (From Wiswell et al. (1994); with permission)



(Yeh et al. 1982). For most infants with MAS, obstruction of the airways with meconium leads to downstream atelectasis (Fig. 47.2) (Wiswell et al. 1994). The juxtaposition of atelectatic and normally aerated lung units is reflected in the patchy opacification typically noted on chest x-ray in MAS (Fig. 47.3) (Yeh et al. 1979).

Experimentally, meconium instilled into the trachea reaches the alveoli within a few hours (Davey et al. 1993; Gooding et al. 1971), and the combination of haemorrhagic alveolitis and surfactant inhibition that follows potentiates the regional atelectasis. Meconium is toxic to the alveolar epithelium (Oelberg et al. 1990; Higgins et al. 1996), causing disruption of the alveolocapillary barrier and an exudative oedema not unlike that seen in acute respiratory distress syndrome. The underlying lung interstitium shows inflammatory cell infiltrate (Tyler et al. 1978; Davey et al. 1993), and there is a cytokine release in part related to complement activation (Castellheim et al. 2005; Jones et al. 1996; Cayabyab et al. 2007). The alveolar oedema potentiates the local atelectasis, causing variable degrees of ventilation-perfusion mismatch, or, worse still, intrapulmonary shunt. Moreover, meconium causes a potent dose-dependent inhibition of surfactant function (Moses et al. 1991; Sun et al. 1993; Herting et al. 2001), and, along with fibrinogen and haemoglobin in the exudate (Fuchimukai et al. 1987; Holm and Notter 1987), impairs the

capacity of endogenous surfactant to reduce surface tension. Stability of alveoli at end expiration is thus compromised (Possmayer 2004), as is the capacity to clear oedema fluid from the air spaces (Carlton et al. 1995). The global consequence of these alveolar disturbances is a reduction in lung compliance (see below).

MAS is frequently accompanied by PPHN (Abu-Osba 1991), with many factors contributing to its development, including low pO_2 and pH, coexistent intrauterine asphyxia and possibly vasoactive substances in the meconium itself (Wiswell and Bent 1993).

The most prominent and consistent physiological disturbances of pulmonary function in MAS are hypoxaemia and decreased compliance. Some degree of hypoxaemia is universal in symptomatic MAS, contributed to by many of the above-mentioned noxious effects of meconium. Disturbances of oxygenation in MAS may relate to atelectasis, overdistension, pulmonary hypertension or a combination of these. A challenging aspect of the management of MAS is to discern which mechanism of hypoxaemia is the predominant one in any given infant at any given time.

47.2.3.3 Lung Mechanics and Functional Residual Capacity

In naturally occurring MAS in animals (Shaffer et al. 1984) and humans (Cayabyab et al. 2007; Yeh et al. 1982; Brudno et al. 1990; Beeram

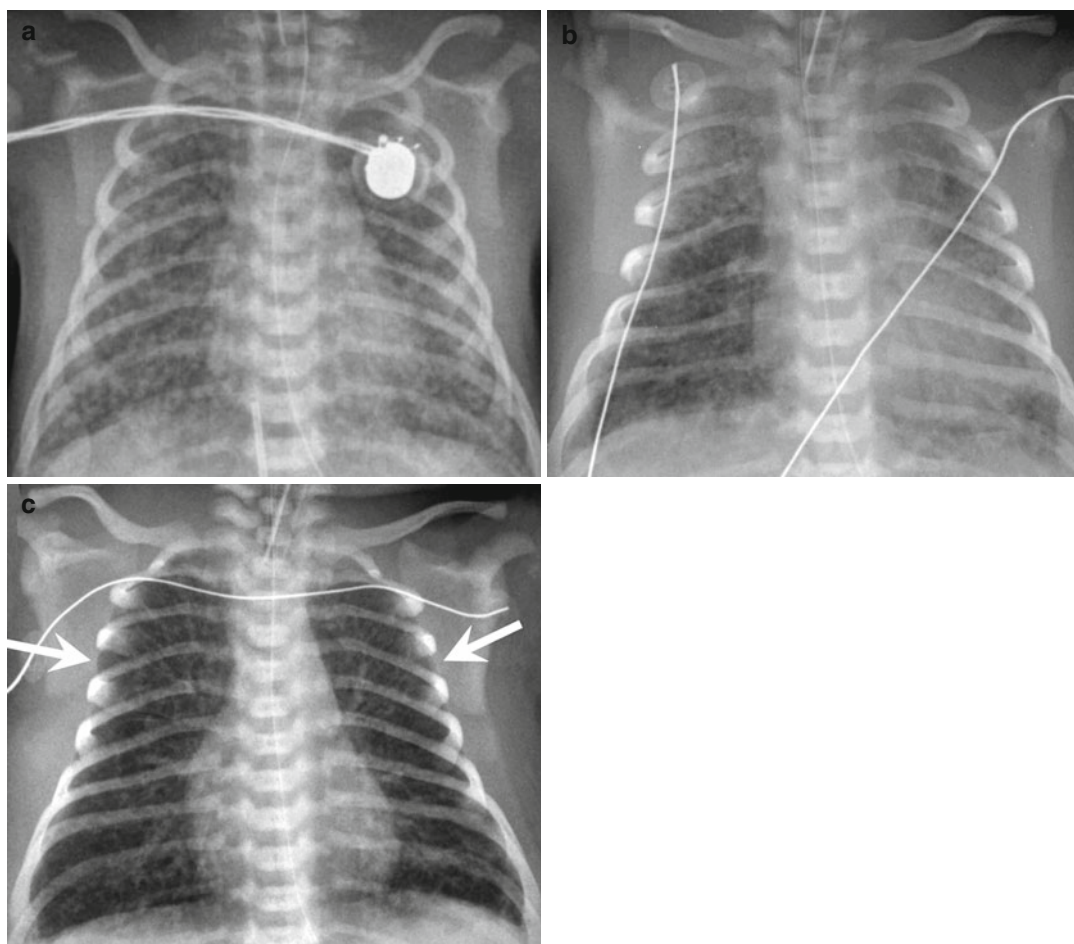


Fig. 47.3 Chest x-ray appearances in ventilated infants with MAS. Panel (a): Typical appearance of MAS showing ‘fluffy’ opacification widespread throughout the lung fields. Panel (b): Marked atelectasis in an infant with pro-

found hypoxaemia. Panel (c): Hyperinflation and gas trapping, with a narrow cardiac waist, flattened diaphragms and intercostal bulging of the lung (*arrows*)

and Dhanireddy 1992; Kugelman et al. 1995; Szymankiewicz et al. 2004), as well as in animal models of MAS (Tran et al. 1980; Davey et al. 1993), lung or respiratory system compliance is significantly impaired. Some studies in experimental animals have indicated that decreased compliance may be related to hyperinflation secondary to ‘ball-valve’ airway obstruction (Tran et al. 1980). In human infants, poor compliance has been noted with low and high FRC, although the only study reporting measurement of both indices simultaneously has been in non-ventilated infants with MAS of mild to moderate severity (Yeh et al. 1982). This study also demonstrated

that most infants with MAS have FRC values in the normal range, with a subgroup showing high lung volumes, in particular, on the second day of life. Undoubtedly, in infants with more severe MAS requiring ventilation, there is the potential for overdistension of relatively unaffected lung regions which, due to their relatively long time constant, may empty incompletely during the ventilator expiratory cycle, especially at fast ventilator rates (Ramsden and Reynolds 1987). Respiratory resistance has also been noted to be increased in some studies, but variations in the technique of measurement make interpretation of these results difficult (ATS-ERS Pediatrics Assembly 1993).

47.2.3.4 Epidemiology

In most cases, MAS has its origin in two prenatal events. The first of these is in utero passage of meconium, and the second is an exaggeration of the normal pattern of fetal respiration (Duenhoelter and Pritchard 1977), to the point where the normal net efflux of fluid from the fetal lung is reversed and meconium gains entry into the lung in an amniotic fluid vehicle. Inhalation of meconium or meconium-stained fluid may also occur as an immediate postnatal event with the first breaths of extrauterine life. The lack of impact of oropharyngeal suction performed prior to the first breath on the risk and severity of subsequent MAS (Vain et al. 2004) suggests that postnatal inhalation of meconium is considerably less important as a cause of MAS, and that most cases are of prenatal origin.

Passage of meconium in utero is frequent (~10–15 %) (Wiswell and Bent 1993), with the most important determinant under normal circumstances being gestational age. Meconium passage occurs in 4 % of infants <38 weeks, 13 % at 39–40 weeks and 25–50 % of infants beyond 42 weeks (Ostrea and Naqvi 1982; Eden et al. 1987) and appears in many post-mature infants to be a physiological event not preceded by in utero compromise. On the other hand, in some instances prenatal meconium passage is clearly linked to fetal distress, with meconium-stained amniotic fluid more likely to occur where there is low fetal pH and/or low Apgar scores (Wiswell and Bent 1993).

The likelihood of MAS developing in the presence of meconium-stained amniotic fluid is also affected by the presence of fetal compromise. Low Apgar score is a very strong predictor of MAS amongst meconium-stained infants, with the odds ratio for MAS in the presence of a 5 min Apgar score <7 being as much as 21 (Wiswell et al. 2000). Risk of MAS is also higher when the liquor is heavily meconium-stained (Wiswell and Bent 1993; Wiswell et al. 2000).

47.2.3.5 Incidence

In the past few decades, there appears to have been a reduction in the incidence of MAS in many centres, at least in the developed world

(Wiswell et al. 1990; Sriram et al. 2003; Yoder et al. 2002; Dargaville and Copnell 2006). The incidence of MAS requiring intubation and mechanical ventilation is now 0.4–0.6 per 1,000 live births (Dargaville and Copnell 2006; Gouyon et al. 2008). Incidence of MAS remains high outside the developed world, with hospital-based studies suggesting an incidence of MAS requiring intubation of 1.4–7 per 1,000 live births (Bhat and Rao 2008; Velaphi and Van Kwawegen 2008).

47.2.3.6 Risk Factors

Amongst all live births, several risk factors for MAS have been identified, with the presence of fetal compromise overshadowing all others. Compared to infants with a 5 min Apgar score of 7 or above, those with a score below 7 had an odds ratio of 52 for the development of MAS requiring intubation (Dargaville and Copnell 2006). Other important risk factors for MAS include advanced gestation (Yoder et al. 2002; Dargaville and Copnell 2006), black or indigenous or Islander ethnicity (Sriram et al. 2003; Dargaville and Copnell 2006; Urbaniak et al. 1996), Caesarean delivery (Dargaville and Copnell 2006; Hernandez et al. 1993) and home birth (Dargaville and Copnell 2006).

47.2.3.7 Stepwise Approach to Respiratory Support

As noted in the sections above, MAS is a disease of many elements, which coalesce into a problematic respiratory syndrome that can be difficult to treat. An approach to respiratory support is set out below.

47.2.3.7.1 Oxygen Therapy

Supplemental oxygen administration is the foundation upon which treatment for MAS is built and, in many less severe cases, will be the only therapy required (Singh et al. 2009b). Some ventilated infants with MAS require high inspired oxygen concentration for long periods, with few apparent adverse effects. Infants persistently requiring an $\text{FiO}_2 > 0.8$ should, however, have measures taken to improve oxygenation (see Table 47.1).

Table 47.1 Approach to hypoxaemia in MAS

If there is marked global or regional atelectasis, with extensive radiological opacification, consider:

- Increasing PEEP to improve end-expiratory lung volume
- Increasing PIP to recruit atelectatic lung units
- Increasing inspiratory time to facilitate the recruiting effect of PIP
- Use of HFOV with sufficient distending pressure to recruit atelectatic lung units
- Use of HFJV with sufficient PEEP to maintain FRC and conventional breath PIP to recruit atelectatic lung units
- Exogenous surfactant
- Lung lavage

If there is obvious gas trapping, with global or regional hyperlucency radiologically, along with distortion of normal anatomy (flattened diaphragms, narrow cardiac waist), consider:

- Decreasing PEEP (but may lose recruitment of areas prone to atelectasis)
- Decreasing inspiratory time and increasing expiratory time
- Use of HFJV with low PEEP, low frequency (240–360 bpm) and minimal CMV breaths
- Use of HFOV with relatively low P_{AW} and low frequency (5–6 Hz)

If there is pulmonary hypertension, with a pre- and post-ductal SpO_2 difference and/or evidence of increased right ventricular pressure, consider:

- Correction of potentiating factors – hypoglycaemia, hypocalcaemia, hypomagnesaemia, polycythaemia, hypothermia and pain
- Bolstering systemic blood pressure to reduce right-to-left ductal shunt – volume expansion and pressor agents
- Improving right ventricular function – inotrope infusion
- Selective pulmonary vasodilators – inhaled nitric oxide

Moment by moment titration of oxygen concentration (or flow) in infants with MAS should be according to SpO_2 level, with a pre-ductal reading to be preferred and the SpO_2 target range being higher (e.g. 94–98 %) than that used in preterm infants. In ventilated infants, oxygen therapy should also be monitored by regular blood gas sampling from an intra-arterial line, preferably in a pre-ductal position in the right radial artery. Suggested target pO_2 range is 60–100 mmHg (pre-ductal). Where there is considerable PPHN, titration of FiO_2 using post-ductal pO_2 values is not advisable.

47.2.3.7.2 Continuous Positive Airway Pressure (CPAP)

Of all infants requiring mechanical respiratory support because of MAS, approximately 10–20 % are treated with CPAP only (Wiswell et al. 2000; Dargaville and Copnell 2006; Singh et al. 2009b). Additionally, around one-quarter of infants requiring intubation with MAS receive CPAP before and/or after their period of ventilation (Dargaville and Copnell 2006). CPAP for such infants can be effectively delivered by bi-nasal prongs or a single nasal prong, typically with a CPAP pressure of 5–8 cm H_2O . Tolerance of the CPAP device may be limited given the relative maturity of infants with MAS, and on occasions the associated discomfort will exacerbate pulmonary hypertension to the point where intubation becomes necessary.

47.2.3.7.3 Intubation

Approximately one-third of all infants with a diagnosis of MAS require intubation and mechanical ventilation (Wiswell and Bent 1993; Cleary and Wiswell 1998). This proportion varies according to how assiduously non-ventilated cases are identified in published series and also depends on ventilation practices of individual units. Indications for intubation of infants with MAS include (a) high oxygen requirement ($FiO_2 > 0.8$), (b) respiratory acidosis, with arterial pH persistently less than 7.25, (c) pulmonary hypertension and (d) circulatory compromise, with poor systemic blood pressure and perfusion (Goldsmith 2008). Except in emergency circumstances, intubation of infants with MAS should be performed with premedication. Significant endotracheal tube leak is a major barrier to effective ventilation in infants with MAS, and in most cases a size 3.5 mm internal diameter endotracheal tube will be required. Once intubated, tolerance of the endotracheal tube will require ongoing sedation with infusions of an opiate (e.g. morphine or fentanyl) (Aranda et al. 2005), possibly supplemented with a benzodiazepine. Additionally, continuation of muscle relaxant drugs is often helpful during the stabilisation period after intubation, particularly in infants with coexistent pulmonary hypertension.

47.2.3.7.4 Conventional Mechanical Ventilation

Despite more than four decades of mechanical ventilation for infants with MAS, the ventilatory management of the condition remains in the realm of ‘art’ rather than ‘science’, with very few clinical trials upon which to base definitive recommendations. Physiological principles and published experience of ventilation in MAS do, however, allow some guiding principles to be put forward for conventional ventilation strategy.

47.2.3.7.4.1 Choosing a Mode of Ventilation

Ventilation mode and the value of patient triggering have been incompletely studied in MAS. Two randomised trials of patient-triggered ventilation have included infants with MAS. One of these found no advantage of synchronised intermittent mandatory ventilation (SIMV) over IMV in 15 infants with MAS (Chen et al. 1997). Another study found, in a group of 93 infants >2 kg birth weight (including an unspecified number with MAS), that use of SIMV was associated with a shorter duration of ventilation compared with IMV (Bernstein et al. 1996). Despite the relative paucity of evidence in favour, it seems logical to use a synchronised mode of ventilation in any spontaneously breathing ventilated infant with MAS. Trigger sensitivity should be set somewhat higher than for a preterm infant and should take into account the possibility of autocycling if there is a tube leak (Bernstein et al. 1995). There have been no clinical trials in patients with MAS comparing SIMV and synchronised intermittent positive pressure ventilation (SIPPV), also known as assist control. Given the propensity for gas trapping in MAS, there is some concern that using SIPPV may lead to high levels of inadvertent positive end-expiratory pressure (PEEP) with resultant hyperinflation. For this reason SIMV may be the most appropriate mode of ventilation in MAS.

47.2.3.7.4.2 Selection of Positive End-Expiratory Pressure

For any newborn respiratory disease, but particularly MAS, application of PEEP must balance the competing interests of overcoming atelectasis while avoiding overdistension. Early observations

of the effect of PEEP suggested the greatest benefit with PEEP settings between 4 and 7 cm H₂O, with higher PEEP settings (8–14 cm H₂O) giving minimal oxygenation benefit (Fox et al. 1975). No more recent clinical studies exist to guide PEEP selection in MAS; physiological principles dictate that if atelectasis predominates (Fig. 47.3b), PEEP should be increased up to 10 cm H₂O, whereas for regional or global hyperinflation (Fig. 47.3c), a lower PEEP (3–4 cm H₂O) may be necessary (Goldsmith 2008). For infants with severe atelectasis, PEEP settings above 10 cm H₂O are likely to increase the risk of pneumothorax (Probyn et al. 2004), and modes of high-frequency ventilation are to be preferred if available.

47.2.3.7.4.3 Selection of Inspiratory Time

As with PEEP, setting inspiratory time in MAS must take into account the balance between atelectasis and overdistension. Term infants have generally longer time constants than their preterm counterparts (Wood 2003) and thus require a longer inspiratory time (around 0.5 s) to allow near-full equilibration of lung volume change in response to the applied peak pressure. Even longer inspiratory times may be useful for lung recruitment during inspiration if atelectasis is prominent.

47.2.3.7.4.4 Selection of Peak Inspiratory Pressure (or Tidal Volume)

Given the reduced compliance, the peak inspiratory pressure (PIP) required to generate sufficient tidal volume in MAS are often high (30 cm H₂O or more). Such pressures may well contribute to a secondary ventilator-induced lung injury in ventilated infants with MAS. Suggested target tidal volume is 5–6 mL/kg. If using a ‘volume guarantee’ mode, the peak pressure limit should be set at or near 30 cm H₂O to allow the ventilator to scale up the PIP when needed to reach the tidal volume target. If PIP is persistently higher than 30 cm H₂O, high-frequency ventilation should be considered, if available.

47.2.3.7.4.5 Selection of Ventilator Rate

Especially if there is gas trapping and expiratory airflow limitation, optimal conventional

ventilation in MAS requires the use of a relatively low ventilator rate (<50) and hence longer expiratory time. This will help to avoid inadvertent PEEP. The resultant minute ventilation must be sufficient to produce adequate CO₂ clearance. An acceptable arterial pCO₂ range is 40–60 mmHg and pH 7.3–7.4, which is achievable in most infants even when there is significant parenchymal disease combined with PPHN (Gupta et al. 2002). Hyperventilation-induced alkalosis, which anecdotally appeared to reduce the need for extracorporeal membrane oxygenation (ECMO) in infants with PPHN (Walsh-Sukys et al. 2000), is no longer practised, in part due to the risk of sensorineural hearing loss (Hendricks-Munoz and Walton 1988).

47.2.3.7.5 High-Frequency Oscillatory Ventilation

Despite the dearth of clinical trial evidence suggesting a benefit (Henderson-Smart et al. 2009), high-frequency oscillatory ventilation (HFOV) has become an important means of providing respiratory support for infants with severe MAS failing conventional ventilation. Published series from large neonatal databases suggest that 20–30 % of all infants requiring intubation and ventilation with MAS are treated with high-frequency ventilation (Dargaville and Copnell 2006; Singh et al. 2009b; Tingay et al. 2007), with most of these receiving HFOV rather than high-frequency jet ventilation (HFJV). Indications for transitioning to HFOV include ongoing hypoxaemia and/or high FiO₂ and, less commonly, respiratory acidosis. In infants with significant atelectasis, adequate lung recruitment may require the application of a mean airway pressure (P_{AW}) considerably higher than on conventional ventilation (up to 25 cm H₂O in some cases), with a stepwise recruitment manoeuvre likely to be the most effective (Pellicano et al. 2009). Once oxygenation has improved, P_{AW} should then be reduced; most infants with MAS requiring HFOV can be stabilised using a P_{AW} around 16–20 cm H₂O, with gradual weaning in the days thereafter (Dargaville et al. 2007). Infants with prominent gas trapping may tolerate the recruitment process poorly, with reductions

in oxygenation and systemic blood pressure and the potential for exacerbation of pulmonary hypertension. Recruitment manoeuvres of some form can still be advantageous in this group, with the benefit becoming apparent when the P_{AW} is reduced.

Choice of oscillatory frequency is critically important in MAS, with experimental studies and clinical experience indicating that frequency should not be higher than 10 Hz and preferably should be set at 8 or even 6 Hz. In experimental models of MAS, high oscillatory frequency (15 Hz) is associated with worsening of gas trapping (Hachey et al. 1998). HFOV can also lend a clinical advantage in infants with significant coexisting PPHN, as the response to inhaled nitric oxide (iNO) is better when delivered on HFOV compared to conventional ventilation (Kinsella et al. 1997). Early reports suggested that up to half of infants with MAS treated with HFOV did not respond adequately and went on to receive ECMO (Carter et al. 1990; Paranka et al. 1995). More recent experience would suggest that only around 5 % of infants treated with HFOV and iNO fail to respond and transition to ECMO (Wiswell et al. 1990).

47.2.3.7.6 High-Frequency Jet Ventilation

The combination of atelectasis and gas trapping that can occur in MAS may be better managed with HFJV than HFOV, with the former technique offering the possibility of ventilation at a lower P_{AW} (Keszler et al. 1986). A number of laboratory investigations have shown HFJV either alone or in combination with surfactant therapy, to be beneficial in animal models of MAS (Keszler et al. 1986; Wiswell et al. 1992, 1994). Clinical studies including infants with MAS appear to confirm the benefit of HFJV compared with conventional ventilation, both in terms of improvement in oxygenation and in avoidance of ECMO (Davis et al. 1992; Engle et al. 1997). Additionally, some infants with MAS failing on HFOV with hypoxaemia and/or respiratory acidosis do show improvements after transition to HFJV using a low frequency (240–360 bpm) and a low conventional ventilator rate (Dargaville (2010), unpublished observations).

47.2.3.8 Rationale for Using Adjunctive Therapies

47.2.3.8.1 Bolus Surfactant Therapy

The pathophysiology of MAS includes inhibition of surfactant in the air spaces, both by meconium and by exuded plasma proteins (Moses et al. 1991; Sun et al. 1993; Herting et al. 2001; Fuchimukai et al. 1987). Preliminary reports of the use of exogenous surfactant given as bolus therapy to ventilated infants with MAS were promising (Auten et al. 1991; Khammash et al. 1993), although it was identified that around 40 % of cases did not respond (Halliday et al. 1996). Four randomised controlled trials of bolus surfactant therapy have been conducted (Findlay et al. 1996; Lotze et al. 1998; Chinese Collaborative Study Group for Neonatal Respiratory Diseases 2005; Maturana et al. 2005), which when analysed together show a benefit in terms of reduction in need for ECMO, but not duration of ventilation or other pulmonary outcomes (El Shahed et al. 2007). In the developed world, bolus surfactant therapy is currently used in 30–50 % of ventilated infants with MAS (Dargaville and Copnell 2006; Singh et al. 2009b). Bolus surfactant therapy should be used judiciously in MAS, choosing infants with severe disease, and treating early, and if necessary, repeatedly (Dargaville and Mills 2005).

47.2.3.8.2 Lavage Therapy

Lung lavage using dilute surfactant is an emerging treatment for MAS that offers the potential of interrupting the pathogenesis of the disease by removal of meconium from the air spaces (Dargaville and Mills 2005). Laboratory studies and preliminary clinical evaluations have indicated that lavage therapy may improve oxygenation and shorten duration of ventilation in MAS (Cochrane et al. 1998; Wiswell et al. 2002; Dargaville et al. 2003). A recent randomised controlled trial of large volume lavage using dilute surfactant in infants with severe MAS noted no effect on duration of respiratory support or other pulmonary outcomes, but did find a higher rate of ECMO-free survival in the treated group (Dargaville et al. 2011). A further clinical trial would be necessary to more precisely define the effect on survival.

47.2.3.8.3 Corticosteroid Therapy

Steroid therapy has been investigated in MAS for more than three decades, with a number of small clinical trials being conducted, none of which have given a definitive result. One recent trial suggested that dexamethasone therapy could dampen the inflammatory response in MAS, as indicated by levels of tumour necrosis factor- α (Tripathi et al. 2007). In the absence of further trials, steroid therapy cannot be recommended as routine therapy in MAS.

47.2.3.8.4 Inhaled Nitric Oxide

Large randomised controlled trials have demonstrated the effectiveness of iNO in term infants with pulmonary hypertension, with a reduction in need for ECMO, and in the composite outcome of death or requirement for ECMO (Finer and Barrington 2006). Each trial included a large subgroup with MAS; overall more than 640 infants with MAS have been enrolled in iNO trials, although few have reported the outcome for MAS separately. The potential value of delivering iNO during HFOV has been highlighted in one trial, in which the proportion of nonresponders was lowest when the two therapies were combined (Kinsella et al. 1997). Currently around 20–30 % of all ventilated infants with MAS receive iNO (Dargaville and Copnell 2006; Singh et al. 2009b), and around 40–60 % show a sustained response (Gupta et al. 2002; Kinsella et al. 1997).

The approach to an infant with MAS and coexistent PPHN should initially focus on optimising the ventilatory management and, in particular, overcoming atelectasis if this is prominent radiologically. The severity of PPHN should be assessed clinically and by echocardiogram if available. If moderate to severe PPHN persists after appropriate ventilatory manoeuvres and the pO_2 remains at less than 80–100 mmHg in FiO_2 1.0 (Kinsella et al. 1997; Wessel et al. 1997), iNO should commence at a dose of 10–20 ppm. Higher doses do not appear to result in better oxygenation (Guthrie et al. 2004).

47.2.3.8.5 Extracorporeal Membrane Oxygenation

Infants with severe MAS have been treated with ECMO since 1976, and MAS has been the

leading diagnosis amongst neonates referred for this therapy (Short 2008). With the advent of newer therapies, the number of infants with MAS treated with EMCO has decreased (Fliman et al. 2006), but survival with ECMO treatment for MAS has remained high (around 95 %) (Short 2008). The usual indication for commencing ECMO is intractable hypoxaemia despite optimisation of the patient's condition with available therapies (including high-frequency ventilation and iNO and bolus surfactant therapy). Degree of hypoxaemia in this setting has generally been quantified using oxygenation index (OI), where $OI = P_{AW} \times FiO_2 \times 100 / PaO_2$. An OI persistently above 40 despite aggressive standard management has been, and remains, an indication for treatment with ECMO where available (UK Collaborative ECMO Trial Group 1996).

47.2.3.9 Classical Complications

47.2.3.9.1 Air Leak

Pneumothorax is a feared complication of MAS which potentiates lung atelectasis and PPHN and compounds the difficulties with management. Around 10 % of all ventilated infants with MAS are reported to have this complication (Wiswell et al. 1990; Dargaville and Copnell 2006). Pneumothorax is associated with an increase in the risk of mortality (Dargaville and Copnell 2006; Lin et al. 2004), in part related to the severity of the associated lung disease, but also to the destabilising influence of the air leak itself. Clinicians should remain attuned to the possibility of pneumothorax in ventilated infants, particularly those prone to gas trapping, and should employ ventilatory strategies to avoid regional and global overdistension wherever possible. Effective treatment requires that air be evacuated from the pleural space immediately once the condition is diagnosed, and then in most instances, an intercostal drainage tube is required to control ongoing air leak.

Other air leak syndromes, including pneumomediastinum and pulmonary interstitial emphysema, are occasionally seen in MAS. Pneumopericardium and pneumoperitoneum are rare. Pneumomediastinum usually requires no treatment unless under significant tension (Masuda et al. 1984). Pulmonary interstitial

emphysema in the setting of MAS at times results in the formation of multiple large cysts and can be extremely difficult to treat. The condition is best managed either with HFJV (see Table 47.1) or HFOV at low frequency (5–6 Hz).

47.2.3.9.2 Pulmonary Haemorrhage

Pulmonary haemorrhage (or, more correctly, haemorrhagic pulmonary oedema) occurs in a small proportion of infants with MAS and can occasionally cause severe destabilisation and hypoxaemia (Berger et al. 2000). Transient application of a high airway pressure is usually necessary to drive this oedema fluid back into the interstitium of the lung. This is best achieved using high-frequency ventilation, with P_{AW} above 30 cm H₂O sometimes required to re-recruit flooded alveoli.

47.2.3.9.3 Chronic Lung Disease

Cases of severe MAS succumbing after a long period of ventilation can have severe distortion of normal lung architecture on post-mortem examination (Chou et al. 1993). Refinements in ventilatory and adjunctive care now mean that fewer infants have long-standing severe chronic lung disease after MAS. Nevertheless, approximately 5–7 % of ventilated infants with MAS remain in oxygen for more than 4 weeks (Dargaville and Copnell 2006; Singh et al. 2009b), and 5 % go home in oxygen (Dargaville and Copnell 2006). A subset of infants who have had MAS in the newborn period will have wheezing and repeated hospitalisations in the first year of life and have demonstrable abnormalities on respiratory function testing (Yuksel et al. 1993). These abnormalities would be expected to largely resolve later in the first decade (see below).

47.2.3.9.4 Comorbidities

Seizures occur in around 10 % of all ventilated infants with MAS, most usually in the context of a coexistent hypoxic-ischaemic encephalopathy (Singh et al. 2009b; Cleary and Wiswell 1998). Circulatory insufficiency is common, and the majority of infants who have severe MAS and coexistent PPHN are treated with inotrope infusions (Dargaville et al. 2011). Multi-organ failure develops in a small proportion of such infants.

47.2.3.10 Short- and Long-Term Outcome

47.2.3.10.1 Mortality

Mortality related to MAS has decreased significantly, with population-based studies suggesting a mortality of 1–2 per 100,000 live births (Sriram et al. 2003; Dargaville and Copnell 2006; Nolent et al. 2004). The case fatality rate in ventilated infants with MAS varies widely in published series (0–37 %) (Cleary and Wiswell 1998) and is influenced by availability of alternative means of ventilation, adjunctive therapies including nitric oxide and ECMO. Approximately one-quarter to one-third of all deaths in ventilated infants with a diagnosis of MAS are directly attributable to the pulmonary disease, with the remainder in large part caused by hypoxic-ischaemic encephalopathy (Dargaville and Copnell 2006; Singh et al. 2009b; Nolent et al. 2004).

47.2.3.10.2 Duration of Ventilation, Oxygen and Hospitalisation

Considering all intubated infants with MAS, median duration of ventilation is 3 days (mean 4.8 days) (Dargaville and Copnell 2006). Infants with more severe disease, requiring at least one of HFV, iNO or bolus surfactant, are ventilated for a median of 5 days (Dargaville and Copnell 2006). Median duration of oxygen therapy and length of hospital stay currently stand at 7 and 17 days, respectively (Dargaville and Copnell 2006).

47.2.3.10.3 Long-Term Outcome

Respiratory compromise after hospital discharge is common in infants who were ventilated with MAS. Up to half of infants will be symptomatic with wheezing and coughing in the first year of life (Yuksel et al. 1993). Older children may exhibit evidence of airway obstruction, hyperinflation and airway hyperreactivity, but appear to have normal aerobic capacity (Swaminathan et al. 1989).

Neurological sequelae following MAS are well recognised (Cleary and Wiswell 1998), and a diagnosis of MAS in the neonatal period confers a considerable risk of cerebral palsy (5–10 %) (Beligere and Rao 2008; Walstab et al.

2004) and global developmental delay (15 %) (Beligere and Rao 2008).

Essentials to Remember

- Atelectasis, overdistension or pulmonary hypertension may all contribute to hypoxaemia in MAS, and it is vital to consider which of these is predominating at any given point in time in an infant who remains hypoxic despite high FiO_2 .
- Overdistension of relatively unaffected lung regions is a serious barrier to effective ventilation in MAS.
- With judicious use of available modes of ventilation and adjunctive therapies, infants with even the most severe MAS can usually be supported without needing ECMO.

47.2.4 Congenital Diaphragmatic Hernia

Desmond Bohn

Educational Aims

- To describe the epidemiology of CDH
- To outline the principles of resuscitation and stabilisation in the delivery suite
- To describe the ventilation techniques with a focus on preventing ventilation-induced lung injury
- To describe the options for surgical repair and the changes in physiology associated with it
- To discuss the importance of increased pulmonary vascular reactivity in CDH
- To discuss the place of extracorporeal membrane oxygenation in the management of CDH
- To outline the main long-term morbidity associated with improved survival

47.2.4.1 Introduction

The management of congenital diaphragmatic hernia (CDH) in the newborn infant has changed radically since the first successful outcomes were reported 60 years ago (Gross 1946). Then it seemed a surgical problem with a surgical solution – do an operation, remove the intestines and solid viscera from the thoracic cavity, repair the defect and allow the lung to expand. CDH in that era was regarded as the quintessential neonatal surgical emergency. The expectation was that urgent surgery would result in improvement in lung function and oxygenation. That approach persisted up to the 1980s when it was realised that the problem was far more complex and involved both an abnormal pulmonary vascular bed and pulmonary hypoplasia. The use of systemically delivered pulmonary vasodilator therapy became a focus of interest in the 1980s with case reports and small case series suggesting improved survival. In the 1990s, based on studies that showed worsening thoracic compliance and gas exchange following surgical repair, deferred surgery and preoperative stabilisation became the standard of care. At the same time, extracorporeal membrane oxygenation (ECMO) was increasingly used either as part of preoperative stabilisation or as a rescue therapy after repair. Other centres chose to use high-frequency oscillatory ventilation (HFOV). Despite all these innovations, the survival rate in live-born infants with CDH did not improve to much more than 50 % in large series published from high-volume centres. However, in the past 10 years, there has been an appreciable improvement in survival to the extent that many centres are now reporting survival rates of greater than 80 %. Probably the biggest impact on this improvement has been the recognition of the role that ventilation-induced lung injury plays in mortality and the need for ECMO rescue. This has ushered in an era of a lung protective or ‘gentle ventilation’ strategy which has now been widely adopted as a standard approach and has largely been responsible for survival rates of 80 % or higher being reported by high-volume centres.

47.2.4.2 Epidemiology

Congenital diaphragmatic hernia is an anomaly that occurs in 1 in approximately 3,000 live

births (Langham et al. 1996). Eighty-five per cent are left sided, and the most common form is the classic posterolateral or Bochdalek hernia. There is a reported incidence of 40–50 % of other malformations in association with CDH, the most common of which are those involving the central nervous system (Tibboel and Gaag 1996). The most important, in terms of prognosis, is congenital heart anomalies. Approximately 11–15 % of CDH infants will have heart defects based on a recent review of the literature, the most common being atrial and ventricular septal defects, conotruncal defects (tetralogy, transposition, pulmonary atresia, double outlet right ventricle) and left ventricular outflow tract obstruction (Lin et al. 2007). Outcome data on this association are limited and confined to case reports or case series (Lin et al. 2007; Cohen et al. 2002; Torfs et al. 1992; Fauza and Wilson 1994). Based on the physiology, hemodynamically significant lesions associated with ventricular outflow tract obstruction (hypoplastic left heart syndrome, tetralogy, coarctation) or those with high pulmonary blood flow (atrioventricular septal defect, large perimembranous ventricular septal defects) will have more impact on mortality compared to atrial and small ventricular septal defects. CDH is also associated with chromosomal abnormalities both in number (Turner’s syndrome, trisomy 13 and 18) and in specific chromosomal aberrations (Fryns syndrome). A rare familial association has also been reported (Frey et al. 1991). There is a rare variant of bilateral absence of the diaphragm which is associated with a fatal prognosis (Gibbs et al. 1997; Jasnosz et al. 1994).

In isolated CDH the spectrum of severity covers a wide range from infants with severe pulmonary hypoplasia and hypoxaemia refractory to conventional and innovative ventilation techniques to those with a much more benign course and minimal blood gas derangements. The degree of pulmonary hypoplasia and the severity of the pulmonary vascular abnormality are the important issues that determine survival (Bohn et al. 1987). Evidence suggests that the lesion includes failure of both alveolar and vascular development to the extent the cross-sectional area of the pulmonary vascular bed is reduced.

47.2.4.3 Delivery Room Resuscitation and Stabilisation

The key principles of successful delivery room resuscitation and stabilisation are based on early intubation and positive pressure ventilation. Bag mask ventilation should be avoided to prevent gut distention. A recent study that measured tidal volume and airway pressure during spontaneous and assisted breathing in newborn infants with CDH immediately after delivery showed that spontaneous breaths with assisted ventilation achieved a higher TV than manual inflations alone (te Pas et al. 2009b). There is increasing evidence that the use of 100 % oxygen has adverse long-term consequences and should be avoided (Davis et al. 2004a). The objective for ventilation should be the establishment of a satisfactory pre-ductal arterial saturation (>85 %) while at the same time avoiding the use of high inflation pressures based on the hypothesis that this may injure the lung. An experimental study in a preterm lamb model of lung disease of prematurity has shown that as few as 6 high-volume lung inflations at the time of delivery results in pulmonary barotrauma and a blunted response to surfactant (Bjorklund et al. 1997). Although this is clearly not the same model as CDH, the lungs are hypoplastic and the potential for secondary injury exists. The objective of positive pressure ventilation should be to limit peak inspiratory pressure to 25 cm H₂O and to target a pre-ductal SaO₂ of >85 % while tolerating hypercarbia (PaCO₂ 45–55 mmHg) if necessary as long as there is a compensated pH (>7.35). Correction, using bicarbonate, if the pH is below that level, may be appropriate. Neuromuscular-blocking drugs are useful during the initial resuscitation, but evidence for their continued or routine use is controversial. Surfactant replacement therapy has also been advocated for infants who present with severe hypoxaemia and low Apgar scores based on some encouraging results in animal models of CDH, but this is not supported by any human data (Logan et al. 2007; Van Meurs 2004). Standard additional procedures should include insertion of a nasogastric tube as well as arterial and central venous lines. Principles for the safe transport of these infants include a

secure airway, gut decompression, adequate vascular access, a compensated pH and a pre-ductal saturation of >85 %.

47.2.4.4 Contemporary Intensive Care Management: CDH as a Cardiopulmonary Disease

The postnatal management of congenital diaphragmatic hernia has evolved from being a surgical problem with a surgical solution through different eras when focus was on the pulmonary vascular abnormalities and most recently on ventilation-induced lung injury. A more holistic approach is to consider CDH as a cardiopulmonary disease (Bohn 2002). The approach in the past has been to make assumptions about pulmonary vascular resistance (PVR) based solely on gradients between pre- and post-ductal saturations and post-ductal PaO₂ measurements. Much more detailed information is available by echocardiography which can inform decision making on the management of pulmonary artery pressure and right ventricular function. This together with skilful ventilator management can result in substantial improvements in survival.

47.2.4.5 Pre- and Postoperative Ventilation

The management of persistent pulmonary hypertension of the newborn (PPHN), including CDH, up to the mid-1990s included the use of hyperventilation to induce an alkalosis, based on a small case series published by Drummond in 1981 which demonstrated that this could reverse or eliminate ductal shunting (Drummond et al. 1981). This approach, which set the tone for the management of PPHN for the next 15 years, was based on observations in only six patients. No prospective trial ever demonstrated that this improved outcome, rather there is now persuasive evidence that it may indeed be harmful in terms of pulmonary barotrauma and cerebral vasoconstriction. As long ago as 1985, a 'permissive hypercapnia' strategy was advocated by Wung in ventilation of infants with PPHN, well before it was introduced into adult medicine (Wung et al. 1985). Several retrospective series of CDH have shown that airway pressure limitation and tolerance of hypercarbia while focusing on pre-ductal

oxygen saturation to be the most important factors in favourably influencing outcome (Bohn 2002; Bagolan et al. 2004; Boloker et al. 2002; Downard et al. 2003; Kays et al. 1999; Wilson et al. 1997; Wung et al. 1995). These series report not only improved survival rates of up to 80 % but also a significant reduction in the need for ECMO support. In the original CDH series, proposing this approach published by Wung et al. (1995) advocated that the key objective of conventional mechanical ventilation should be to keep PIP ≤ 25 cm H₂O while maintaining a pre-ductal SaO₂ >85 %. Patients were managed without muscle relaxation and a chest drain. In this situation, ductal shunting can be tolerated as long as right heart function is adequate. This is based on lessons learned from newborn infants with cyanotic congenital heart disease that a normal lactate, a mixed venous oxygen saturation (SvO₂) of >70 % and the absence of a metabolic acidosis are compatible with adequate oxygen delivery.

Many centres are now opting to use HFOV as a way of avoiding barotrauma and report improved survival using this approach together with deferred surgery (Bohn 2002; Bagolan et al. 2004; Bouchut et al. 2000; Cacciari et al. 2001; Desfrere et al. 2000; Kamata et al. 1998; Migliazza et al. 2007; Miguët et al. 1994; Ng et al. 2008; Reyes et al. 1998; Skari et al. 2004; Somaschini et al. 1999). This had not been our experience when we were using hyperventilation as part of our strategy to reverse ductal shunting with HFOV as a rescue mode in the 1980s (Azarow et al. 1997). When we performed a detailed analysis of post-mortem findings in 1999, the most striking finding was not only the degree of pulmonary barotrauma and haemorrhage in the ipsilateral lung but also in the contralateral (Sakurai et al. 1999). We believed that our error was to use HFOV with the ventilation strategy that incorporated lung recruitment as was commonly used in other forms of neonatal lung disease. The post-mortem study of findings in 68 non-surviving infants with CDH from an era when we were using HFOV with a high mean airway pressure (>20 cm H₂O) showed that the high mortality (50 %) could be partially attributed to pulmonary barotrauma causing damage to

hypoplastic lungs (Sakurai et al. 1999). There was a high incidence of air leak as well as histology showing pulmonary haemorrhage and hyaline membrane formation. CDH does not represent a recruitable lung, and attempts to use a high mean airway pressure (MAP) are likely to cause secondary lung injury. More recent case series have recommended MAPs no higher than 14–16 cmH₂O (Desfrere et al. 2000; Miguët et al. 1994; Somaschini et al. 1999). We have now changed our philosophy on the use of HFOV from a rescue mode to an early intervention strategy in order to limit lung injury when PIP exceeds 25 cm H₂O on conventional ventilation. The peak-to-peak pressures (amplitude) are adjusted to achieve a PaCO₂ in the range of 35–45 mmHg with a pH in the range of 7.35–7.45 as long as the pre-ductal SaO₂ is >85 %. Mean airway pressure is limited to 14–16 cmH₂O. The adoption of this strategy has been associated with a significant improvement in survival in our centre since 1995 (Bohn 2002).

47.2.4.6 Surgical Repair and Thoracic Compliance in CDH

For many years there was an assumption that surgical repair would improve gas exchange by relieving compression of the ipsilateral lung which formed the basis for surgical repair. Formal measurements of thoracic compliance and blood gases before and after repair not only showed that this was not so but also, on the contrary, demonstrated a deterioration which was associated with a rise in PaCO₂ actually for the same ventilator settings (Fig. 47.4) (Sakai et al. 1987). There are several possible explanations for this finding. Firstly, the abdominal cavity may be somewhat small because the viscera have been in the chest during fetal life and surgical repair and closure restricts movement of both diaphragms. Secondly, the repair itself can stretch the diaphragm especially if the defect is large and a patch is not used. These findings resulted in resetting the priorities for the timing of surgical repair which have changed substantially in the past two decades and provided the rationale for delayed surgery and preoperative stabilisation which has now become widely accepted practice. The decision on timing of

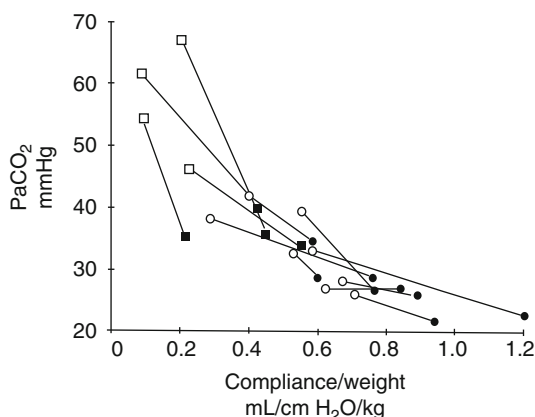


Fig. 47.4 Correlation between compliance and PaCO_2 levels. Survivors: (●) preoperative and (○) postoperative; nonsurvivors: (■) preoperative and (□) postoperative (From Sakai et al. (1987); with permission)

repair is based on evaluating the infant's haemodynamic and pulmonary profile. Surgery should be delayed until such time as there has been a reduction in PVR, and satisfactory ventilation can be maintained with low PIP and inspired oxygen requirements. Infants with mild forms of CDH with a low PIP and minimal shunting can be repaired within the first 24–48 h of life, while infants who are labile with right-to-left shunting should have surgery deferred on a day-to-day basis until such time as they stabilise, even if this requires protracted periods of preoperative ventilation. Where HFOV is used, surgery should be delayed until such time as the infant can be switched back to conventional ventilation and managed with peak airway pressures of <25 cm H_2O as this meets a definition of stability. We do not undertake surgical repair in infants with pre-ductal hypoxaemia and hypercarbia which cannot be reversed by therapies outlined in the previous sections.

In terms of surgical repair, Gortex, Marlex or biosynthetic porcine patches are commonly used to close large defects that cannot be closed by primary repair without major distortion of the thorax, but these are associated with a significant recurrence rate (Hajer et al. 1998; Moss et al. 2001; St Peter et al. 2007). Data from the CDH Registry has shown that there is a relationship between defect size and outcome (Lally et al.

2007). Reduction of the hernia with replacement of the abdominal viscera is frequently associated with difficult abdominal wound closure and an adverse change in respiratory system compliance. The use of an abdominal silo to counter this problem has been suggested in some studies (Kyzer et al. 2004; Rana et al. 2008). There is no indication to insert pleural drains at the time of surgery, and they are only needed in the postoperative period in the event that there is an accumulation of pleural fluid that results in mediastinal shift or a contralateral pneumothorax (Wung et al. 1995). There has been an increasing trend to opt for non-invasive surgical repair techniques. Although this can be done successfully, there are a significant number of cases where the procedure has to be changed to an open reduction or there has been a recurrence of the hernia (Kyzer et al. 2004; Chiu and Hedrick 2008; Cho et al. 2009; Guner et al. 2008; Yang et al. 2005). Given this and the fact that the non-invasive technique is unlikely to shorten the ICU length of stay or the time on mechanical ventilation, this approach is difficult to rationalise except on the basis of the cosmetic effect.

47.2.4.7 Pulmonary Vascular Management

Increased pulmonary vascular resistance (PVR) is an almost universal finding in CDH even when not clinically manifest by right-to-left shunting at ductal level. The diagnosis of PPHN in CDH is usually made on the basis of a pre-/post-ductal saturation gradient. However, as this only occurs when pulmonary artery pressure exceeds systemic, in the absence of this finding, there is little clinical information on the level of pulmonary artery pressure (PAP). Therefore, the information obtained by echocardiography is becoming an increasingly important tool in the management of CDH, firstly to exclude an associated congenital heart defect but also to assess the degree of pulmonary hypertension. Important prognostic information may also be available in predicting outcome. In a single-centre retrospective review by Dillon, all infants with subsystemic PA pressures survived (Dillon et al. 2004). The cardinal echo features of systemic or near systemic

PAP are flattening of the intraventricular septum, development of tricuspid regurgitation (TR) and right-to-left or bidirectional shunting at ductal level. The presence of pre-ductal desaturation implies that there is a right-to-left shunt at atrial level, and the PA pressure is well above systemic throughout the entire cardiac cycle. The presence of a TR jet allows the operator to actually estimate right ventricular pressure. Identification of the ductus is also important because as long as this is widely patent, it allows the right ventricle to decompress and prevents right heart failure when the pressure becomes suprasystemic. A new finding of pre-ductal desaturation, in a previously stable infant, might indicate that the ductus has closed or become restrictive and, if confirmed by echo, would warrant a trial of prostaglandin (PGE_1) in order to open the ductus and prevent right ventricular failure (Buss et al. 2006; Inamura et al. 2005; Kinsella et al. 2005). Furthermore, in light of studies that have shown that left ventricular (LV) mass is decreased in infants with CDH (Schwartz et al. 1994; Siebert et al. 1984) leading to compromise of LV function, there is an additional rationale to maintain ductal patency (Kinsella et al. 2005).

Although undesirable, ductal shunting can be tolerated by the infant as long as pre-ductal saturations are maintained in the 80–85 % as this reflects very adequate cerebral oxygenation. Indeed, saturations in this range are a common scenario in many forms of cyanotic congenital heart disease. The use of hyperventilation to reverse this is likely to do more harm than good in that it exchanges ventilator-induced lung injury for better systemic oxygenation.

Infants who demonstrate significant ductal shunting or elevated right ventricular pressures can be tried on inhaled nitric oxide (iNO) although evidence for an outcome benefit, in terms of survival, is lacking. A randomised trial of the use of iNO in PPHN which included infants with CDH showed that they were the group that responded least well with no impact on survival or the use of ECMO (The Neonatal Inhaled Nitric Oxide Study Group (NINOS) 1997). However, a more accurate assessment of the response to iNO is by cardiac echo, and if a reduction of right

ventricular pressure is documented, the therapy is worth continuing, accepting that it is unlikely that the dramatic reductions in PVR, seen in other forms of PPHN, will occur. Ductal shunting and low systemic pressures can also be improved by the use of inotropic support, particularly if there is right heart failure. There is also increasing interest in the use of phosphodiesterase inhibitors in the treatment of PPHN, specifically the PDE5 inhibitor sildenafil. A recent open-label study of an IV infusion of the drug in hypoxic neonates showed an improvement in OI (Steinhorn et al. 2009). There are also some small case series of sildenafil being used successfully in the management of sustained pulmonary hypertension in CDH (Keller et al. 2004; Noori et al. 2007; Rocha et al. 2008).

There are other novel therapies that have been tried in treatment of pulmonary hypertension. Arginine vasopressin is now commonly used in the treatment of vasodilated shock, and it may have some interesting effects on the pulmonary circulation. Retrospective data suggests that in this situation it increases systemic pressure while causing a reduction in pulmonary artery pressure in adults (Dunser et al. 2001). It has also been used successfully in the management of two newborn infants with suprasystemic pulmonary artery pressures in the immediate postoperative period after repair of total anomalous pulmonary venous connection (Scheurer et al. 2005). There is also a single case report of the use of the vasopressin analogue terlipressin in successfully reversing ductal shunting in an infant with CDH who was resistant to iNO, alkalosis and inotropic therapy (Papoff et al. 2009).

As well as pulmonary hypertension occurring in the immediate postnatal period, there are a certain number of infants who survive and are weaned from mechanical ventilation where PVR remains elevated necessitating further intervention (Dillon et al. 1995; Iocono et al. 1999; Schwartz et al. 1999). The use of inhaled nitric oxide delivered by nasal cannula has been reported in the treatment of sustained pulmonary hypertension (Kinsella et al. 2005). Finally, there is a single case report describing the use of imatinib, an anti-platelet-derived growth factor drug

in the successful treatment of an infant with CDH and suprasystemic pulmonary artery pressures (Frenckner et al. 2008).

47.2.4.8 Extracorporeal Membrane Oxygenation

Extensive experience of the use of ECMO in the management of CDH has been accumulated since the first case series were published in the 1980s (Bartlett et al. 1986). The Extracorporeal Life Support Organization (ELSO) database shows that it has been used to support 5,700 infants with an overall survival of 51 % (The Extracorporeal Life Support Organisation 2009). This is the least favourable outcome for ECMO support in all forms of acute respiratory failure in infants. Despite the better outcomes demonstrated in the UK randomised trial, the survival rate in the 35 CDH infants enrolled in the study was very poor with only 4 survivors out of 18 in those who were randomised to ECMO surviving to hospital discharge (UK Collaborative ECMO Trail Group 1996).

When it was first introduced, ECMO was originally used in the rescue of infants with severe hypoxaemia after surgical repair. Many centres now opt to use ECMO as part of a deferred repair strategy, together with other therapies such as iNO and HFOV, to stabilise the infant prior to repair and perform the surgery either just prior to weaning from support or after decannulation. Data from the CDH Registry suggests that repair post ECMO is associated with the best outcome (Bryner et al. 2009). The latest innovation in extracorporeal support has been the so-called EXIT to ECMO strategy where prenatally identified high-risk infants are cannulated immediately after delivery while still connected to the placenta (Bouchard et al. 2002; Kunisaki et al. 2007). The most commonly used cannulation technique is veno-arterial, although some centres have reported success with the veno-venous approach (Austin et al. 2004; Dimmitt et al. 2001; Heiss et al. 1995; Kugelman et al. 2003). Venous cannulation pre-repair may be problematic because of caval distortion when the liver is herniated. The duration of support is frequently prolonged, the average in the ELSO database being 10 days

with a duration up to 50 days. Morbidity in terms of pulmonary and neurocognitive function post ECMO in survivors is significant (Van Meurs 2004; D'Agostino et al. 1995; Davis et al. 2004b; McGahren et al. 1997; Nijhuis-van der Sanden et al. 2009; Stolar et al. 1995). It is also a highly costly therapy which, in one series, was reported to be \$365,000 per survivor in 1995 US dollars (Metkus et al. 1995). The indications for the use of ECMO in CDH are far from clear as indeed are the data which suggest that there is a clear benefit in terms of survival and long-term outcome associated with its use.

There is a wealth of case series and database material which puts ECMO in a favourable light. Many centres with a historically high mortality rate in the 1990s (>50 %) reported an improvement in survival with the introduction of delayed repair and the use of ECMO as a rescue therapy (D'Agostino et al. 1995; Frenckner et al. 1997; Heiss et al. 1989; Semakula et al. 1997; vd Staak et al. 1995; West et al. 1992). However, this must be now placed into the context of reports of survival rates of >80 % either from centres where ECMO is not available (Bagolan et al. 2004; Al-Shanafey et al. 2002) or where there has been the adoption of alternate management strategies which has led to a significant reduction in the need for ECMO (Bohn 2002; Boloker et al. 2002; Kays et al. 1999; Wilson et al. 1997; Miguet et al. 1994; Azarow et al. 1997; Mettauer et al. 2009). In terms of large case series from high volume (>10 cases/year), the evidence for improved outcome with ECMO is not persuasive. In a retrospective review of over 400 infants with CDH from The Children's Hospital, Boston, and The Hospital for Sick Children, Toronto, outcome was compared between 1981 and 1994 during an era where the major changes were deferred surgery and the use of ECMO (Wilson et al. 1997; Azarow et al. 1997). In the Boston series, ECMO was used in 50 % of cases as the rescue mode, while in Toronto HFOV was used with only very occasional resort to ECMO (1 %). The survival rate in the two institutions was the same (53 % vs. 55 %). Since the introduction of a lung protective ventilation strategy, the survival rate has risen in both institutions to 80 % or higher. Most

high-volume centres are experiencing a reduction in ECMO use in CDH (Kays et al. 1999; Wilson et al. 1997; Mettauer et al. 2009), which parallels the declining numbers in all forms of neonatal respiratory failure (Hintz et al. 2000). Although many reasons for this have been suggested, a major contributing factor has been the change in ventilation practice. This was confirmed when data from the ELSO Registry between 1988 and 1997 was analysed (Roy et al. 2000). This showed a reduction in the annual numbers of neonatal ECMO support from 1991 onwards which coincided with an increased use of HFOV and iNO. Perhaps of more significance, the mean level of PIP prior to the initiation of ECMO had fallen from 47 ± 10 cm H₂O in 1988 to 39 ± 12 cmH₂O in 1997.

Does the use of ECMO either as part of a preoperative stabilisation algorithm or as a rescue therapy improve the survival rate in CDH? A Cochrane review of published studies concluded that there is evidence for short-term efficacy, but it is unclear whether there is long-term benefit as defined as improved survival without increase morbidity (Elbourne et al. 2002). Perhaps the more relevant question now is: in an era of 'gentle ventilation', does the use of ECMO result in not only improved survival but without increase morbidity? The hypothesis could be tested in a prospective multicentre RCT, but it is unlikely to happen because of lack of equipoise. One of the major difficulties is selection criteria and what constitutes the need for ECMO. Traditionally an oxygenation index (OI) >40 has been used and was the entry criteria for the UK randomised trial (UK Collaborative ECMO Trial Group 1996), but as it is most frequently calculated from a post-ductal PaO₂, it is largely influenced by a right-to-left shunt at ductal level. Previous studies that used the relationship between PaCO₂ and ventilation parameters to define severity are no longer relevant in an era when permissive hypercapnia ventilation is widely practised. The most frequently cited criterion is now 'failure of medical management' which is obviously difficult to define. Does this mean that all patients should be considered eligible for ECMO, exclusive of those with other major congenital anomalies?

There clearly is a subset of patients with pulmonary hypoplasia which is incompatible with life and will result in failure to separate from ECMO. Some studies have excluded patients based on failure to demonstrate a post-ductal PaO₂ of >100 mmHg (Stolar et al. 1988) or a pre-ductal SaO₂>85 % at some stage of their resuscitation or stabilisation (Boloker et al. 2002). In our centre we would only consider the use of ECMO in those infants who decompensate with severe pre-ductal hypoxaemia and right-to-left shunting due to high PVR, where we are unable to maintain a pre-ductal SaO₂>85 % and who fail to respond to a management strategy that includes HFOV, iNO, inotropic support or opening the ductus with PGE₁ (Bohn 2002; Buss et al. 2006). We would not offer ECMO to infants with severe pulmonary hypoplasia, as defined by severe hypercarbia in the immediate postdelivery period and the inability to demonstrate a pre-ductal SaO₂ of >85 % at some stage after initial resuscitation. Since 1995 we have used ECMO in only 18 infants with only 6 survivors but still have an overall 80 % survival.

47.2.4.9 Outcome and Long-Term Follow-Up

The outcome in newborn infants presenting within the first 24 h of life has changed significantly in the past 10 years from 50 % to now 80 % or higher in high-volume centres. There is a price tag for this improvement in survival which has been increase in morbidity in those infants who previously would have died. There has been a rise in the number of reports of survivors with chronic lung disease, recurrent or residual pulmonary hypertension, gastroesophageal reflux, oral feeding aversion, poor weight gain, hernia recurrence, pectus excavatum, scoliosis, pulmonary hypertension, neurosensory hearing loss and delayed neurodevelopment (Kinsella et al. 2005; Stolar et al. 1995; Bernbaum et al. 1995; Chiu et al. 2006; Hunt et al. 2004; Jaillard et al. 2003; Jakobson et al. 2009; Koivusalo et al. 2008; Morini et al. 2008; Muratore et al. 2001a, b; Rasheed et al. 2001; Stolar 1996; Stolar et al. 1990; Van Meurs et al. 1993; Vanamo et al. 1996a, b, c). The incidence of morbidity is higher in these infants treated

with ECMO and those requiring patch closure (Jaillard et al. 2003; Lund et al. 1994). One of the major areas of concern is that of neurological morbidity. In a study published from Boston Children's Hospital in 1994, 30 % of CDH infants where ECMO was used had abnormal CT scans (Lund et al. 1994). These abnormalities are independent of ECMO use. A report by Hunt using MRI showed a high incidence of ventriculomegaly, white matter and basal ganglia abnormalities in a series of CDH survivors where ECMO was not used (Hunt et al. 2004). A long-term follow-up study from this institution has shown an increased incidence of oral motor and visuomotor control in 10–16 year old CDH patients compared to controls (Jakobson et al. 2009). The underlying causes of which are probably multifactorial and include perinatal asphyxia and hypoxaemia, alkalosis to treat ductal shunting and ECMO support.

As might be predicted there is a high incidence of problems of gastroesophageal reflux (GER) and feeding difficulties in severe CDH infants who are now surviving. The incidence depends on the era studied and the length of follow-up (Koivusalo et al. 2008; Muratore et al. 2001b; Stolar et al. 1990; Arena et al. 2008). Data from a multidisciplinary follow-up clinic has shown a 32 % incidence of GER with 19 % of patients undergoing fundoplication. Twenty-four per cent had aversion to oral feeding and 56 % were below the 25th percentile for weight despite the use of gastrostomy tubes (Muratore et al. 2001b). More extended and detailed follow-up studies have shown that between a third and a half of patients have oesophageal abnormalities by endoscopy (Koivusalo et al. 2008; Arena et al. 2008).

In terms of pulmonary function, one can anticipate a difference in morbidity in an era of improved survival of more severe forms of CDH. Studies of pulmonary function and cardiorespiratory exercise done on adolescents also from our centre who came from an era when the survival rate was 50 % showed some degree of airway obstruction but near normal exercise capacity compared with normal controls (Trachsel et al. 2005, 2006). However, follow-up

studies from Boston Children's Hospital where they report 90 % survival show prolonged ICU stays and duration of ventilation with 16 % of infants oxygen dependent at the time of discharge (Muratore et al. 2001a). Two studies have reported that 4 % of patients in their series have required tracheostomy (Jaillard et al. 2003; Bagolan and Morini 2007). Obstructive airways disease is seen in up to 25 % of survivors and chronic lung disease in up to 22 % (Jaillard et al. 2003; Ijsselstijn et al. 1997). Chest and musculoskeletal deformities are also being documented more frequently in multidisciplinary follow-up clinics, and these include pectus excavatum and scoliosis (Vanamo et al. 1996a; Lund et al. 1994; Nobuhara et al. 1996). Many of these complications are more frequently seen in infants where the defect is large and requires a patch repair and the use of ECMO, which again reflects the severity of the disease (Lally et al. 2007; Stolar 1996; Muratore and Wilson 2000). Infants with CDH in this new era require more than the traditional surgical follow-up clinic visits, and many centres, including our own, have now developed multidisciplinary clinics involving general surgeons, chest physicians, dieticians, neonatal follow-up specialists and cardiologists (Lally and Engle 2008). It is only with this coordinated approach that these medically challenging infants will receive the appropriate care for their ongoing problems.

47.2.4.10 Summary

Congenital diaphragmatic hernia is a complex disease with, until this decade, a 50 % mortality due to a pathophysiology which combines pulmonary hypoplasia and pulmonary vascular disease. The introduction of delayed surgical repair and ECMO in the 1990s was associated with an improved survival in centres with previous high mortality rates. Equivalent improvements were seen in centres where HFOV was used as a rescue therapy. There has been a marked improvement in survival with the widespread adoption of lung protective ventilation strategies but at the cost of significant morbidity in infants with hypoplastic lungs and large diaphragmatic defects. The challenge facing those involved in

postnatal management of CDH, especially in centres that offer ECMO, is to decide which infants have the capacity to survive without major morbidity, in particular, neurodevelopmental outcomes. The challenge facing those who advocate prenatal intervention, in an era of 80–90 % survival, is to demonstrate that the predictors they use are robust, easily implemented across centres and are reproducible. If they are, then they need to show in a carefully designed RCT, which includes standardised postnatal management which incorporates current best practice, that tracheal occlusion reduces morbidity. Finally, there is a striking difference in survival in the CDH Registry (68 %) and the >80 survival reported in high-volume centres. Given the fact that CDH is a complex cardiorespiratory disease and that the Canadian Neonatal Network has shown that there is a relationship between volume and outcome (Javid et al. 2004), a strong argument can be made for care of these infants to be regionalised to high-volume centres where multidisciplinary, highly specialised management is available.

Essentials to Remember

- CDH is a cardiorespiratory disease that requires information obtained by cardiac echo to help guide management.
- The lungs in CDH are dysplastic and therefore liable to secondary injury with high pressure positive pressure ventilation.
- High-frequency oscillation and ECMO are both effective rescue therapies, at least in the short term. HFOV with high mean airway pressure can cause lung damage. ECMO provides lung rest and allows time for reduction in PVR.
- Due consideration needs to be given to the degree of pulmonary hypoplasia before choosing ECMO as an option.
- Many infants with severe forms of CDH have major morbidity at long-term follow-up. The emphasis needs to be placed the quality of survival.

Outline of Principles of Management

Resuscitation

ET tube placement with minimal bag mask/ventilation
 Vascular access
 Gut decompression by nasogastric tube
 Ventilation objectives: pre-ductal $\text{SaO}_2 > 85\%$ and $\text{pH} > 7.3$ with $\text{PIP} \leq 25 \text{ cm H}_2\text{O}$

Cardiopulmonary management

Ventilation

Conventional ventilation

Objective: pre-ductal $\text{SaO}_2 > 85\%$ $\text{pH} > 7.3$
 $\text{PIP} \leq 25 \text{ cm H}_2\text{O}$

High-frequency oscillatory ventilation (HFOV)

Objective: pre-ductal $\text{SaO}_2 > 85\%$
 $\text{MAP} 14\text{--}16 \text{ cm H}_2\text{O}$

Pulmonary vascular management

Cardiac echo

Exclude CHD
 Assess RV function
 Estimate PA pressure
 Identify the ductus and assess shunting

Trial of inhaled nitric oxide for patients with increased RV pressure

47.3 Respiratory Failure of Non-pulmonary Origin

47.3.1 Apnoea of Prematurity

Alastair A. Hutchison

Educational Aims

- To describe the key features of the central control of breathing, the coordinated output to the motor effectors, the resultant mechanical events resulting in ventilation and the nature of the nervous and chemical feedbacks to the controller
- To describe the importance of behavioural state in fetal 'breathing'
- To describe apnoea in terms of breathing homeostasis and its limits

- To describe apnoea of prematurity, its different categories and its association with oxygen desaturation and bradycardia and thus potentially with life-threatening tissue hypoxia
- To describe the pathophysiology of apnoea of prematurity in terms of the central circuitry and its outputs, the responses to blood gases, the associated reflex bradycardia, the motor responses to afferent inputs and the upper airway protective and exaggerated responses
- To describe the clinical presentation and differential diagnosis of apnoea of prematurity
- To describe the avoidance of clinical factors that can aggravate apnoea of prematurity and its non-pharmacologic and pharmacologic therapies
- To describe the specifics of caffeine therapy including recommended dosages, efficacy, cessation of therapy and benefits on long-term outcome
- To describe the natural history of apnoea of prematurity, the preparation for safe discharge home, the indications for home monitoring and the lack of a firm association with SIDS
- To describe the concerns about long-term morbidity with recurrent preterm apnoea and the advisability of follow-up care

47.3.1.1 Introduction

When you can't breathe, nothing else matters.
– American Lung Association Motto.

47.3.1.1.1 Breathing, Central Control and Fetal Development

Breathing consists of motor acts that enable tidal ventilation for gas exchange. Immediately at birth the newborn employs intricate breathing patterns that establish and maintain airway volume

and attain ventilation. Thereafter, throughout life the normal breathing pattern, eupnoea, can be gentle tidal breathing that is involuntary and hardly sensed, but many other breathing patterns are employed in normal conditions. Thus, an expanded view of normal breathing is that it consists of centrally controlled coordinated muscular activities which aim to ensure that the airway is protected and has optimal supra- and sub-glottic volumes to maintain homeostasis and provide a stable platform to enable ventilation with ensuing efficient gas exchange and transport (Hutchison 2007). Normal breathing involves central coordination with other motor acts, e.g. swallowing, speech and walking.

Breathing control is primarily determined by the intrinsic nature of the central nervous system (CNS) controller and is modified by integration of all inputs (Fig. 47.5). Two features of central control deserve emphasis. There is a redundancy to the circuitry, with alternative drives and pathways, and there is a motor control hierarchy: rapid airway protection takes precedence over control of absolute airway volume, which in turn takes precedence over relative tidal volume changes. Control of breathing is exercised by the coordinated activities of the nasal, pharyngeal, laryngeal and pump muscles which, in concert with lower airway smooth muscle tone that adjusts airway wall stiffness, alter the transairway pressure gradients. The result is that tidal ventilation occurs simultaneously with the control of total airway volume, which adjusts airway pressure critical for patency, central feedback and likely drive threshold (Adrian 1933). Airway and chest wall neural feedback is rapid (milliseconds) and crucial for homeostasis, enabling the controller to adjust flow within a breath and match motor outputs with the structural characteristics of the different parts of the respiratory system and their associated mechanics. Feedback from blood gaseous and chemical sensors occurs within seconds.

...thoracic gymnastics in preparation for the great extrauterine function of atmospheric respiration.

– John W. Ballantyne, 1902.

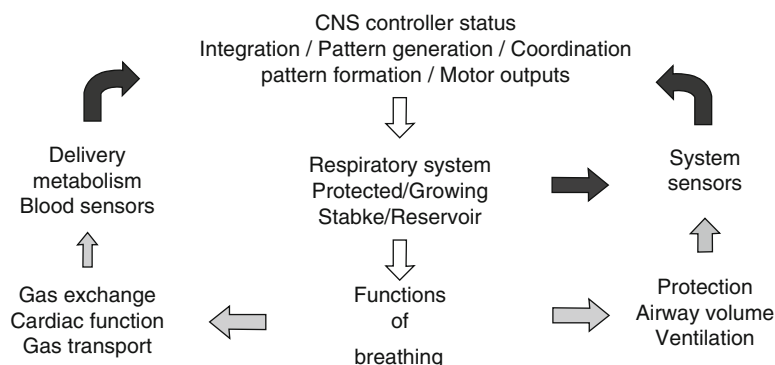


Fig. 47.5 Breathing control. This diagram of the central control of breathing shows its functions both in enabling ventilation with gas exchange and the simultaneous maintenance of airway patency and respiratory system

homoeostasis. The central generation and formation of motor breathing patterns involve integration of all sensory inputs in a hierarchical manner

Fetal ‘breathing’ develops when gas exchange is placental and blood oxygen tension is low. Central state is a dominant factor. In fetal sheep, in the high-voltage state, phasic diaphragmatic activity is absent and laryngeal narrowing occurs (Harding 1994). In the low-voltage state, the laryngeal and diaphragmatic activities pattern is similar to that seen postnatally. Both state-related fetal ‘breathing’ patterns are important for lung growth (Harding 1994). Fetal hypercapnia augments ‘breathing’ muscle activities mainly in the low-voltage state (Harding 1994). In contrast, hypoxia, acting at a pontine site, inhibits fetal diaphragmatic activity in the low-voltage state (Harding 1994).

Breathing patterns and apnoea can be viewed as a spectrum/continuum (Fig. 47.6). Throughout life, rapid changes in pattern are dependent upon the status of the central circuitry, its response hierarchy and its different inputs. Central setting of optimal homoeostatic limits must vary constantly with inputs sensing changes in growth and in the individual’s internal and external environments. It is speculated that during sleep, ‘virtual’ central conditions allow the limits to be reset/tuned (Hutchison 2007).

47.3.1.2 Apnoea of Prematurity

... They seem to do the most unreasonable things with their respiration ...

– Kenneth Cross, 1954

47.3.1.1.2 Apnoea, Breathing and Apnoea: A Spectrum of Homoeostasis and Limits

Apnoea is a lack of tidal airflow. Transient lacks of airflow are seen in patterns with glottic closure, e.g. during swallowing, defecating, lifting, coughing, yawning, crying or vocalising. Apnoea occurs with a minimal fall in the carbon dioxide tension (PCO_2) to below the apnoeic threshold (Khan et al. 2005). Brief apnoeas are typified by the brain’s subsequent ability to return quickly to muscle activities that ventilate the airway. Clinical apnoea is a persistent lack of airflow without a spontaneous return to breathing.

47.3.1.2.1 Definition and Types of Apnoea

Apnoea of prematurity is associated with physiological characteristics and pathological conditions found in the preterm infant born at <37 completed postmenstrual weeks. Its incidence is inversely related to gestational age (Henderson-Smith 1981). Brief cessations of airflow lasting a few seconds are common in sleep and may represent a transient return to fetal life. Apnoea demanding attention and meriting the clinical diagnosis of apnoea of prematurity is that lasting 15–20 s or that accompanied by bradycardia, cyanosis or pallor. Apnoea is categorised into

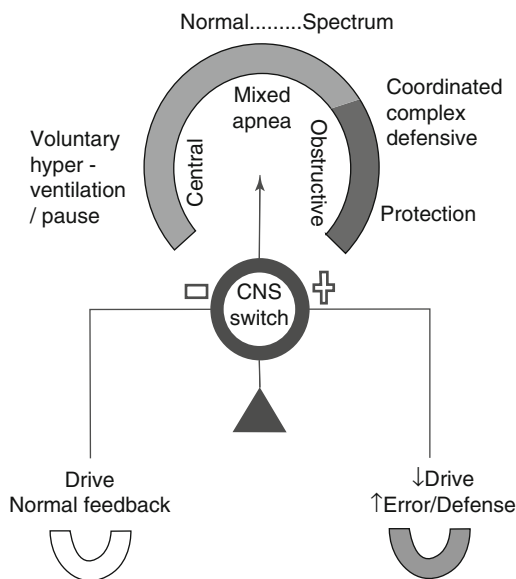


Fig. 47.6 Spectrum of breathing and apnoea. This diagram shows the spectrum of breathing patterns used in daily life including coordination with complex acts such as swallowing and coughing. A centrally controlled pattern switch can rapidly alter the breathing patterns from ones typified in expiration by a more open glottis to ones characterised by a more closed glottis. This occurs transiently in airway volume maintenance, airway protection and speech and is determined by central drive/status and afferent inputs. Expiratory laryngeal closure increases as central drive decreases. It is postulated that in mixed apnoea a switch from central apnoea to obstructive apnoea accompanies a progressive decrease in central drive and that this may be enhanced by a decrease in airway volume during central apnoea with an open glottis

different types. Central apnoea (incidence ~10–25 %) is a lack of tidal airflow accompanied by a lack of pump muscle activity (with or without an open glottis). Obstructive apnoea (~10–20 %) is an absence of tidal airflow accompanied by upper airway obstruction, which can commence in expiration and continue despite pump muscle activity and in the subsequent neural expiration. Mixed apnoea (~50–75 %) is both central and obstructive apnoeas occurring serially, usually in that order. Bradycardia (heart rate <100/min) usually follows the onset of apnoea of prematurity. Oxygen saturation values fall (<85 %) and can produce cyanosis. An associated pallor can

indicate the occurrence of a dive reflex response with preferential blood flow to the heart, brain and adrenals but diminished blood flow to other important organs, e.g. the gut. The newborn brain is more tolerant than the adult to hypoxia, but if apnoea is ongoing, death results.

47.3.1.2.2 Pathophysiology

47.3.1.2.2.1 Central Circuitry and Output Determinants

Rostral and caudal CNS structures influence the control of breathing patterns (Feldman and Del Negro 2006; Rybak et al. 2008). Lesioning studies in animals have identified that, at a minimum, eupnoea requires a pontomedullary neuronal network (Rybak et al. 2008). When both upper pontine respiratory neuronal groups (PRG) and vagal afferents are removed, the lower pontine-medullary output is apnoeic, a pattern typified by prolonged inspiratory drive. The generation of signals for coordination of laryngeal and diaphragmatic activities appears to be dependent upon an intact lower pons (Hutchison and Speck 2003). Inspiratory and pre-inspiratory neurons involved in rhythm generation have been identified in the ventral medullary pre-Bötzinger and parafacial regions, respectively. Neurons in the Bötzinger complex exert mainly expiratory control (Feldman and Del Negro 2006). Specific types of premotor medullary neurons have been classified by their signal shapes and timings. Their actions result in a central breathing cycle consisting of three phases: inspiration, post-inspiration and expiration (Feldman and Del Negro 2006). Mechanical changes following these outputs are seen well in grunting (see Sect. 4.1). Protective, mechanical and speech-related changes occur quickly within a breath; thus, phase-switching and pattern-switching neurons are important (Rybak et al. 2008) (Fig. 47.6).

Apnoea of prematurity is associated with incomplete brain development, including decreased cell synapses, dendrites, myelination and brainstem conduction (Darnall et al. 2006). Gene abnormalities are reported in the central hypoventilation syndrome (Abu-Shaweesh and

Martin 2008). Neurotransmitters (γ -aminobutyric acid (GABA), adenosine, prostaglandin E, serotonin, endorphins, catecholamines, glutamate) affect respiratory-related neuronal function (Darnall et al. 2006). The neurochemistry in preterm infants favours neuronal inhibition over excitation. In animals, prostaglandin E production can be triggered by the cytokine IL-1 β , while adenosine stimulates GABA production (Abu-Shaweesh and Martin 2008). Metabolism is increased by hyperthermia and decreased by hypothermia. Both hypothermia and hyperthermia can decrease breathing, suggesting that hypothermia decreases excitation more than inhibition and that hyperthermia augments the dominant intrinsic inhibitory pathways and their inputs. Thus, the importance of temperature homeostasis is emphasised.

Central apnoea may result from altered PRG input (Hutchison and Speck 2003). When the PRG is removed from decerebrate cats, the response to an expiratory airway load is a pattern similar to central apnoea with an open glottis. In this circumstance, expiratory flow will occur passively until the relaxation volume (V_r) is reached (see Chap. 4.1, Fig. 4.6). Preterm infants actively maintain sub-glottic volume above their low V_r when awake, but during central sleep apnoeas the sub-glottic volume can decrease. This is especially seen in REM sleep when all types of apnoeas are more common and longer and can be associated with profound bradycardia. Central apnoea with glottic closure can also occur, e.g. in some human newborns who are depressed at birth, in preterm lambs (Praud and Reix 2005) and in gasping animals with exposure to acute cerebral hypoxia/ischaemia (Hutchison et al. 2002). Gasping is typified by short diaphragmatic bursts and long expirations with glottic closure. Initially, this incremental breathing pattern (see Sect. 4.1) maintains sub-glottic volume, which is probably critical in autoresuscitation (Hutchison et al. 2002). In lambs, when central depression results in prolonged expiratory apnoea, glottic adductor activity persists until all muscle activity ceases (Praud and Reix 2005). During mixed apnoea,

obstructive upper airway closure commences before diaphragmatic activity and its associated fall in airway pressure (Idiong et al. 1998) and thus appears to be due to centrally altered laryngeal or pharyngeal muscle activities (Idiong et al. 1998; Upton et al. 1992). Obstructive apnoea is due to insufficient pharyngeal opening pressure, which reflects an imbalance between factors that decrease pharyngeal patency (see Sect. 4.1) and the central motor output that dictates a compensatory increase in muscle tone. In the preterm infant, pharyngeal collapse can occur passively with neck flexion or actively in sleep, when pharyngeal wall muscle tone can be low (Thach and Stark 1979). Expiratory laryngeal closure, triggered by a low lung volume, could play a role by reducing intrapharyngeal pressure below its critical value for patency.

47.3.1.2.2.2 Central Responses to Blood Gases and Apnoea of Prematurity

Throughout life, hypocarbia decreases the central drive to breathe (Khan et al. 2005), and during the associated hypopnoea/apnoea, laryngeal adductor activity (glottic closure) is found (Jounieaux et al. 1995; Kuna et al. 1993). The apnoeic threshold is higher in preterm infants with apnoea (Gerhardt and Bancalari 1984), making apnoea more likely with a fall in PCO_2 , e.g. with normal activity, sighing. Hypercapnia increases ventilation, but the response is depressed by accompanying hypoxia (Rigatto 1986) and can be accompanied by expiratory laryngeal closure (Eichenwald et al. 1993). At high PCO_2 levels apnoea can occur (Alvaro et al. 1992). Marked hypercapnia may act via central inhibition of respiratory muscle output and/or by inducing chest wall distortion that can trigger apnoea with laryngeal closure. The preterm infant's response to hypoxaemia may or may not start with a transient increase in ventilation, which, if present, is dependent upon carotid body integrity. A decrease in central output to the diaphragm follows; this decrease is attenuated in non-rapid eye movement sleep (Rigatto 1986). Hypoxia can result in periodic breathing and then apnoea (Rigatto 1986). The responsiveness of the

carotid body is depressed after birth but recovers within 2 weeks (Abu-Shaweesh and Martin 2008). Repeated exposure to hypoxaemia postnatally may augment the carotid body sensitivity to hypoxaemia with a resultant hyperventilation, followed by hypocarbia and decreased ventilation (Al-Matary et al. 2004; Nock et al. 2004). These cycles may produce periodic breathing and apnoea. However, prenatal exposure to cigarette smoke may diminish the response to hypoxaemia (Gauda et al. 2004; Schneider et al. 2008), and exposure to hyperoxia at critical periods of development can inhibit carotid body development in animals (Gauda et al. 2004). Diminished stimulatory responses to hypoxaemia have been found in preterm infants (Gauda et al. 2004). Thus, central integration of both increased and decreased carotid body inputs may promote apnoea (Gauda et al. 2004).

47.3.1.2.2.3 Sinus Arrhythmia and Reflex Bradycardia

Vagal cardiac efferent output decreases in inspiration when airway vagal afferent input increases. Therefore, heart rate increases during inspiration, while it slows during expiration – sinus arrhythmia. The heart rate changes help maintain a constancy of cardiac output and blood pressure. Augmented ventilation in respiratory distress can produce cardiac output volume swings detected as pulsus paradoxus (Goldstein and Brazy 1990). During apnoea, vagal afferent input falls and vagal cardiac efferent output increases; thus, the onset of bradycardia can be immediate. Bradycardia in older preterm infants with apnoea follows the onset of a decrease in oxygen saturation, reflecting the importance of central integration of vagal afferent and chemoreceptor inputs (Poets 2003) (see Sects. 4.1.4.2 and 47.3.1.2.2.5). Vagal efferent activity occurs in swallowing, urinating and defecating and can be accompanied by bradycardia.

47.3.1.2.2.4 Motor Responses to Chest Wall and Airway Inputs

Active maintenance of sub-glottic volume is noted in the newborn, whose elastic chest wall

is ideal for growth and atraumatic birth. Chest wall distortion, inward movement that threatens airway volume, occurs easily and stimulates chest wall afferents that inhibit phrenic activity (intercostal-phrenic reflex) and/or produce glottic closure. Newborn infant motor responses to vagal afferents are easily elicited (Thach 2001). Lower airway slowly adapting receptors (SARs) detect within-breath volume/stretch, while rapidly adapting irritant receptors (RARs) detect distortion/deflation. C-fibre receptors, associated with the pulmonary vasculature, detect chemical changes. In animals, the SAR inputs stimulate the chest wall and diaphragmatic pump muscles during inspiration until peak afferent activity is reached when inspiration is inhibited. Increased vagal afferent feedback accompanies a large inflation and triggers expiratory apnoea – the Hering-Breuer inflation reflex, a response modulated by airway CO₂ in animals. After a large inflation, abdominal expiratory muscle activity is triggered – the Hering-Breuer expiration reflex. Prevention of inspiration by airway occlusion causes a fall in upper and lower airway vagal input, prolonging inspiration. During partial vagal blockade, inflation produces a second inspiratory effort – Head's paradoxical reflex. Prevention of expiration by airway occlusion maintains vagal afferent input, thus prolonging expiratory time. In adult animals, when airway volume is considerably reduced, irritant receptor stimulation triggers an inspiration – the Hering-Breuer deflation reflex. However, irritant receptor input in preterm infants, with deflation or with tracheal stimulation, can result in apnoea (Fleming et al. 1978; Hannam et al. 1998). A cough response is only noted after 34 weeks postmenstrual age (Fleming et al. 1978).

The Hering-Breuer and Head reflexes may act to optimise lung inflation without tissue damage during inspiration and tailor expiratory time for a given expired volume. The stretch receptors may also act to increase central neuronal activity during expiration such that inspiration begins at a higher level of expiratory vagal input and thus peaks sooner, signalling an earlier cessation of tidal inspiration and promoting

respiratory rate (Al-Matary et al. 2004). There is support for Head's viewpoint. Infants use laryngeal and diaphragmatic means of maintaining higher absolute airway volumes and breathe faster (Sect. 4.1) (Thach 2001). In the preterm neonate, atelectasis/deflation post-extubation is associated with apnoea (Hannam et al. 1998). A lower end-expiratory volume (EEV) is noted in REM sleep and in apnoeic infants (Poets 2003). Furthermore, in lambs breathing through a tracheostomy, absence of laryngeal control of EEV is associated with apnoea (Johnson 1979). Airway pressure support after birth is the mainstay for reversal of apnoea and bradycardia, the latter being used in initial stabilisation as a sign to indicate the need for airway volume support. After birth, the intensivist employs the 'open lung (airway) approach' during artificial ventilation. Failure to maintain sub-glottic airway volume when the preterm infant is on a ventilator results in desaturation/bradycardia (Bolivar et al. 1995). This stresses that, when handling the endotracheal tube and/or moving the preterm infant's thorax, the maintenance of sub-glottic airway volume is important.

47.3.1.2.2.5 Upper Airway Protective and Exaggerated Interactive Central Responses

Stimulation of protective receptors, e.g. laryngeal chemoreceptors with superior laryngeal nerve (SLN) afferents, can rapidly interrupt ventilation and close the larynx (Davies et al. 1988). In immature humans and animals, the SLN inputs can instigate apnoea and bradycardia, although a re-distribution of blood flow to the heart, brain and adrenals also occurs – the dive reflex response (Abu-Shaweesh and Martin 2008; Daly 1997). This response to SLN input decreases with advancing age but can be rekindled by a concurrent central depression or an upper airway infection (Daly 1997). The coexistence of central inhibition (e.g. with sedation or hypo-/hyperthermia), followed by SLN stimulation (e.g. at intubation) and then hypoxia, can produce an exaggerated and potentially lethal response, even in the adult (Daly 1997) (Sect. 4.1). This stresses

the roles of central status and the motor response hierarchy in determining pattern (Fig. 47.7).

47.3.1.2.3 Clinical Aspects

47.3.1.2.3.1 Presentation and Differential

Diagnosis

Apnoea can present on the first day of life and is virtually universal in preterm infants born at <28 weeks gestational age (Fig. 47.8) (Henderson-Smart 1981). The severity of apnoea is defined by its duration, the degrees of associated oxygen desaturation and bradycardia, and the type of therapeutic intervention provided, from minimal stimulation to total respiratory support. The assessment of the apnoeic patient consists of the nose-to-diaphragm then the head-to-toe approach. Apnoea of prematurity is differentiated from periodic breathing, a repetitive series of pauses in breathing separated by a crescendo-decrescendo pattern of breaths. Periodic breathing in normal preterm infants is considered benign, but it can be associated with hypocarbia, hypoxia and CNS hypoxia/ischaemia and with a fall in sub-glottic airway volume (Khan et al. 2005; Rigatto 1986). Conditions resulting in apnoea, including structural lesions (Brazy et al. 1987), are considered before a diagnosis of idiopathic apnoea is made (Fig. 47.9). Upper airway contact with food or with gastric contents can result in apnoea, but episodes of gastroesophageal reflux do not appear to be temporally linked to apnoea. In animals, prior upper airway exposure to acid can alter the response to subsequent mechanical loads (Sant'Ambrogio et al. 1998). Thus, the clinical impression that the two are related may be indirect. Pre-existing anaemia exacerbates the apnoeic response to SLN stimulation in animals and is important in postoperative apnoea (Cote et al. 1995). However, blood transfusion therapy for apnoea of prematurity is debated.

47.3.1.2.3.2 Therapy

Specific therapy is given for the conditions listed in Fig. 47.9, e.g. a patent ductus arteriosus (PDA) resulting in hypoxaemia and pulmonary oedema that can trigger lower airway receptors resulting in apnoea. Conditions that can enhance apnoea

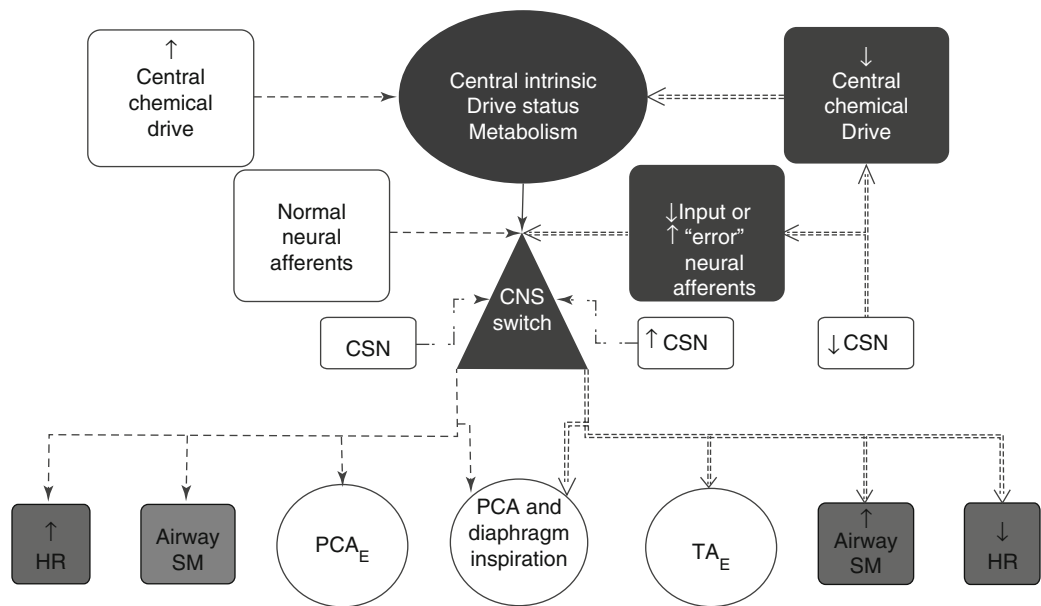


Fig. 47.7 Afferent interactions and the motor response hierarchy. This diagram illustrates how factors influencing motor pattern may interact. Sudden decreases in any excitatory input can alter the balance affecting the outputs to the heart, airway smooth muscle and laryngeal and diaphragmatic muscles producing a more protective pattern (*right side of diagram*). The motor response determining expiratory glottic closure is seen as being determined primarily by the central drive/status, amplified secondly by decreased or error signals in neural afferent inputs and

amplified thirdly by input from carotid body stimulation. Thus, increased carotid body stimulation can amplify an existing pattern. By contrast, a sudden decrease in carotid body input can trigger a switch to a protective pattern. This provides a possible explanation for the proposed roles of both increased and decreased carotid inputs in the genesis of apnoea with glottic closure. *CNS* central nervous system, *CSN* carotid sinus nerve, *HR* heart rate, *Airway SM* airway smooth muscle, *PCA_E* expiratory posterior cricoarytenoid, *TA_E* expiratory thyroarytenoid

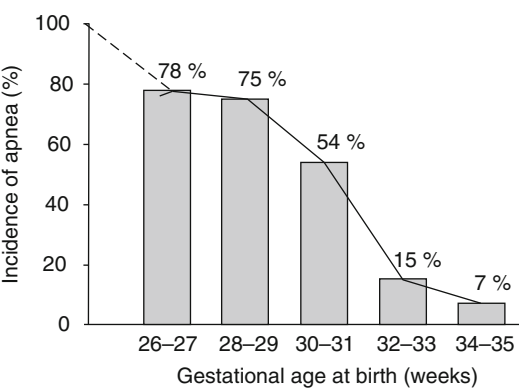


Fig. 47.8 Incidence of apnoea of prematurity. The incidence of apnoea of prematurity increases inversely with the gestational age at birth, being virtually universal in the preterm infant <28 weeks (Modified and reproduced with permission from Henderson-Smart (1981))

are avoided. Hyperoxia can diminish recovery from SLN stimulation in lambs and, with altered carotid chemosensitivity, will increase apnoea (Al-Matary et al. 2004). Careful attention is paid to nasal patency (secretions, proper prong size and attachment of nasal continuous airway positive pressure [NCPAP] device), environmental temperature, correct neck posture (neck flexion) and abdominal distention (air in the stomach, correct positioning of gastric tube, a tight diaper forcing abdominal contents into the chest). Apnoea and bradycardia or bradycardia alone during feeding is usually a benign condition that responds to cessation of the suck/swallow stimulus.

The importance of central ‘drive’ and airway stability/patency as causative factors in apnoea

Fig. 47.9 Aetiology of apnoea of prematurity. Multiple physiological and pathological conditions affect central nervous system (CNS) control and are associated with an increased propensity to apnoea of prematurity

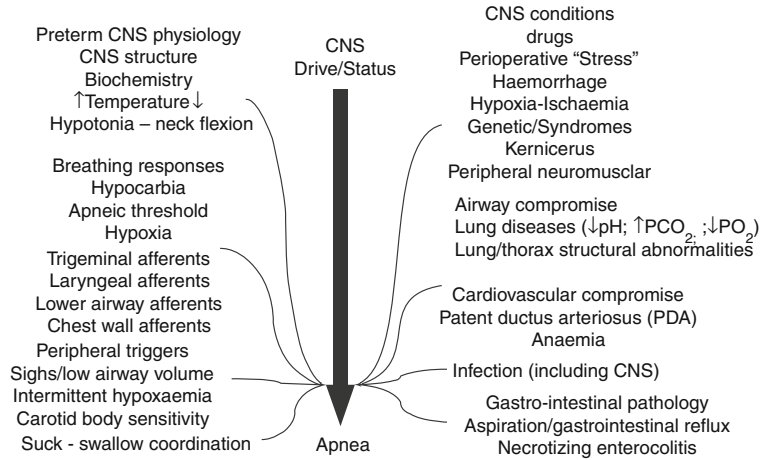


Table 47.2 Therapies for apnoea of prematurity

Effective therapies for idiopathic apnoea	Comments
Physiological stimulation	
Tactile stimulation	Used for minor apnoea
Air cushion	Infrequently used
Inhaled low-concentration CO ₂	Experimental (Abu-Shaweesh and Martin 2008)
Pharmacologic stimulation	
Xanthines	Safe; serum concentration monitoring not needed; ↓ bronchopulmonary dysplasia and ↑ neurodevelopment
Caffeine used in recommended dosing	↓ Postoperative apnoea in former preterms up to ~60 postmenstrual weeks
Theophylline	Bronchodilator properties may be useful
Doxapram	In high dose ↑ seizures; rarely used
Respiratory support	
Nasal cannulae: high flow	Alternative to NCPAP but applied pressure not monitored; used in weaning from NCPAP
Nasal CPAP	Mainstay of therapy; modern device available with low work of breathing Mixed apnoea > central apnoea
Non-invasive positive pressure ventilation	May be useful; more trials awaited
Invasive artificial ventilation	Final resort: has risks of ‘endotrauma’

of prematurity is reflected in the main forms of therapy, namely, peripheral tactile stimulation, xanthine therapy and respiratory airway support (Table 47.2). Xanthine therapy primarily enhances central drive and treats central apnoea (Table 47.3), while NCPAP therapy maintains airway stability and thus prevents mixed apnoea (Miller and Martin 2004). However, caffeine therapy enhances breathing peripherally by improving diaphragmatic function, while NCPAP

therapy enhances central drive by increasing airway vagal feedback and decreasing oxygen saturation variability that may stabilise carotid body feedback.

Despite appearing as a ‘simple’ therapy, NCPAP requires care in its application and excellent bedside monitoring and nursing (Hutchison and Bignall 2008). Laboratory and clinical studies strongly support the use of a modern NCPAP device (Hutchison and Bignall 2008;

Table 47.3 Caffeine effects and side effects

Effects	Side effects
Competitive antagonism of adenosine receptors (A_1 and A_{2a})	↑ Irritability (restlessness) ↑ Jitteriness
Inhibition of phosphodiesterase (minor)	↑ Seizure tendency
Mobilisation of cellular calcium (at high dose)	↑ Diuresis/dehydration
↑ Central 'drive': ↑ minute ventilation ↓ Threshold to hypercapnia	↑ Gastric aspirates ↑ GI intolerance (– gastric acid)
↑ Pulmonary blood flow; ↓ BPD	↑ Tachycardia, arrhythmias
↑ Skeletal muscle and myocardium activity	↑ Hyper-/hypoglycaemia
↑ Metabolism (– O_2 consumption)	↑ Failure to gain weight
↑ Neurodevelopment (recommended doses)	↑ Sleeplessness

Pantalitschka et al. 2009). Weaning from NCPAP is little studied. In general, when an infant is receiving <30 % supplementary oxygen, a switch to high-flow nasal cannulae can be made. The advantage of nasal cannulae lies in their ease of use. The disadvantages are that the airway pressure they generate is not monitored and there may be increased infectious risks. Severe apnoea can warrant invasive mechanical ventilation but involves the complications of 'endotrauma' (Hutchison and Bignall 2008). There is interest in non-invasive positive pressure ventilation (NIPPV) for apnoea, and larger trials are awaited (Hutchison and Bignall 2008; Pantalitschka et al. 2009). Since coordination between the upper airway and pump muscles is critical, NIPPV is applied synchronously with the central outputs to the breathing muscles (Jounieaux et al. 1995); this may be difficult during sleep.

Caffeine therapy with a loading dose of 20 mg/kg followed by 5–6 mg/kg/day produces therapeutic serum concentrations (8–20 mcg/L) independent of the patients' gestational age between 24 and 35 weeks and of their renal and liver functions over wide ranges (Leon et al. 2007). Thus, monitoring of serum caffeine concentrations is unnecessary if the recommended dosing is used. Tachycardia with caffeine can result from a pharmacodynamic effect. It resolves with cessation

of therapy despite a normal serum concentration. Slightly higher and significantly higher caffeine dosing regimens have been used. The latter regimen increased successful weaning from a ventilator (Steer et al. 2003). Concerns about the extensive use of caffeine relate to its action as an antagonism of adenosine, a body-wide mediator of vasodilatation, which is involved in neurodevelopment. However, a controlled trial of early postnatal administration (<10 days) of caffeine versus placebo found that those receiving caffeine in recommended doses had less bronchopulmonary dysplasia (by 10 %) and improved cognitive outcome (by 5 %) (Schmidt et al. 2007; Schmidt et al. 2006b). Adenosine blockade may still be problematic. Caffeine therapy has been linked to necrotising enterocolitis, albeit weakly. Preterm infants are susceptible to white matter injury and thus at increased risk when cerebral blood flow is low (Darnall et al. 2006). If an infant on caffeine therapy develops hypocarbia during ventilatory support, any hypocarbia-associated decrease in cerebral perfusion may be aggravated.

Caffeine therapy is started regularly in infants born at <28 weeks gestational age, and in more mature infants, it is prescribed based upon an increased frequency of minor apnoea, the occurrence of severe apnoea or the presence of respiratory support. Cessation of caffeine therapy is attempted when the apnoea-free infant reaches 32 weeks postmenstrual age. This is successful ~80 % of the time (Spitzer 2002) ensuring a sufficient period for caffeine elimination prior to a hospital discharge decision. Recurrence of apnoea off caffeine may indicate that the apnoea is not idiopathic, e.g. infection related (Darnall et al. 1997).

47.3.1.2.3.3 Natural History/Discharge/Home Monitoring

The duration of apnoea is inversely related to the postmenstrual age at birth. In general, apnoea is absent by 37–40 weeks in those born at >28 weeks postmenstrual age (Darnall et al. 1997; Eichenwald et al. 1997). By contrast, for those born at <28 weeks, apnoea can persist up to 44 weeks postmenstrual age (Darnall et al. 1997; Eichenwald et al. 1997). Home

Table 47.4 Indications for home monitoring

Persistent apnoea and bradycardia (43 weeks)
Apnoea and bradycardia with gastroesophageal reflux
Apnoea and bradycardia with other pathology
Xanthine therapy
Home oxygen – bronchopulmonary dysplasia
Tracheostomy
Home ventilator

monitoring is indicated under certain circumstances (Table 47.4). There is no evidence for an association between apnoea of prematurity and SIDS, nor has monitoring for apnoea of prematurity been shown to affect the incidence of SIDS (Darnall et al. 2006). If caffeine therapy has been discontinued and the infant has been free of apnoea and bradycardia for 5–7 days, then discharge is not delayed and home monitoring is not prescribed. Infants should adopt a ‘back to sleep’ posture prior to discharge and be tested in a car seat. Families should receive regular SIDS counselling advice, including the avoidance of sleeping in situations where the infant can be compressed or have their upper airway blocked.

47.3.1.2.3.4 Prognosis/Follow-Up

Recurrent preterm apnoea may result in short-term and/or long-term morbidity (Abu-Shaweesh and Martin 2008; Darnall et al. 1997). However, no definitive proof exists that apnoea of prematurity per se causes neurodevelopmental delay, as it is almost impossible to control for the multiple confounding intrinsic and extrinsic factors that can influence brain development in the neonatal period and thereafter. Ongoing apnoea in infancy requires investigation and treatment. Follow-up of high-risk preterm infants and provision of required interventions and educational assistance are advised.

Essentials to Remember

- Breathing consists of motor acts that enable ventilation and maintain airway stability.
- Breathing muscle activities can alter rapidly to ensure airway protection or coordinate with other simultaneous

motor functions. Afferent inputs monitor breathing rapidly.

- Breathing patterns and apnoea can be viewed as a spectrum.
- Apnoea, a lack of tidal airflow, can be physiological or pathological.
- Apnoea of prematurity is categorised into central, mixed and obstructive types. It is often accompanied by bradycardia and oxygen desaturation. Thus, severe apnoea is life-threatening.
- Apnoea results from changes in the central outputs to the muscles of breathing and changes induced by altered intrinsic/extrinsic, central/peripheral and neural/chemical inputs.
- Apnoea is exaggerated when upper airway afferents are stimulated during central depression. This can be evident during intubation of the sedated patient.
- Conditions associated with clinical apnoea are excluded before a diagnosis of idiopathic apnoea of prematurity is made.
- Apnoea can recur postoperatively in former preterm infants up to ~60 post-menstrual weeks, and this is exaggerated with anaemia. Perioperative caffeine therapy may prevent this apnoea.
- Management includes avoiding factors that trigger apnoea and non-pharmacologic and pharmacologic therapies, the latter usually with caffeine which, using recommended dosing, has short-term and long-term respiratory and neurodevelopmental benefits.
- Knowledge of the natural history of apnoea of prematurity and caffeine pharmacokinetics allows for the planning of safe home discharge and home monitoring, if required.
- Follow-up for interim medical care and neurodevelopmental evaluation is advised.

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Educational Aims

- Describe and contrast the original and new forms of bronchopulmonary dysplasia
- Describe and discuss different definitions of bronchopulmonary dysplasia
- Present the issues and discuss some of the principles for the management of infants with bronchopulmonary dysplasia

48.1 Bronchopulmonary Dysplasia

Eduardo Bancalari and Nelson Claure

48.1.1 Clinical Presentation

The original publication on bronchopulmonary dysplasia (BPD) by Northway and collaborators described a group of preterm infants who after prolonged mechanical ventilation developed chronic respiratory failure and characteristic radiographic findings (Northway et al. 1967). The lung damage was attributed primarily to the use of aggressive positive-pressure ventilation and high inspired oxygen concentrations. Today, with the widespread use of antenatal corticosteroids and the use of postnatal surfactant and less

aggressive mechanical ventilation, this severe form of BPD has been replaced by a milder form that presents in the more immature infants who frequently have only mild initial respiratory disease (Charafeddine et al. 1999; Parker et al. 1992; Rojas et al. 1995). Therefore, these infants are not exposed to the very high airway pressures or oxygen concentrations, the two main factors in the pathogenesis of the original form of BPD. This milder form of the disease has been described as “New BPD.” This new presentation has created some inconsistencies and confusion in the definition and the diagnostic criteria of BPD (Bancalari et al. 2003).

The severe form of BPD was usually seen in infants who had severe respiratory failure from the time of birth and received aggressive ventilation and prolonged exposure to high inspired oxygen concentrations. These infants had characteristic changes in their chest radiographs and remained on ventilation and supplemental oxygen for long periods of time. This BPD was characterized by severe pulmonary damage that included emphysema, atelectasis, and fibrosis and marked epithelial squamous metaplasia and smooth muscle hypertrophy in the airways and in the pulmonary vasculature. These changes were associated with severe respiratory failure with airway obstruction, pulmonary hypertension, and cor pulmonale. This presentation is uncommon today, but there are still some infants who have

this course and end up with severe respiratory failure, pulmonary hypertension, and marked alterations in their chest radiographs. The radiographs of infants with the milder forms of BPD show a more diffuse pattern reflecting loss of volume or increased lung fluid. Occasionally they also have dense areas of segmental or lobar atelectasis or pneumonic infiltrates but they do not show the areas of severe overinflation characteristic of the original BPD. These different clinical and radiographic manifestations reflect the different pathogenic process that underlines the new presentation of BPD.

This milder form of BPD seen more frequently today is characterized mainly by increased lung fluid, a diffuse inflammatory response, and by a striking decrease in alveolar septation and impaired vascular development (Abman 2000; Coalson et al. 1995; Husain et al. 1998; Jobe 1999; Margraf et al. 1991; Thibeault et al. 2003). These changes are more compatible with an arrest in lung development than with mechanical injury. It is not clear to what extent this arrest in lung development is secondary to the exposure of the premature lung to gas breathing versus the effects of overdistension and oxygen toxicity. Additional factors including incomplete lung development, inflammatory processes due to ante or postnatal infections, (Groneck et al. 1994; Groneck and Speer 1995; Hannaford et al. 1999; Pierce and Bancalari 1995; Watterberg et al. 1996; Yoon et al. 1997) and the exposure of the immature pulmonary vasculature to increased blood flow because of a persistent ductus arteriosus (Gonzalez et al. 1996; Marshall et al. 1999) are also implicated in the pathogenesis of the new BPD.

48.1.2 Definition

There has been a striking lack of uniformity in the diagnostic criteria for BPD among clinicians and in the literature. This explains some of the variation in the reported incidence of BPD among different centers. A major problem with most of the definitions of BPD is that they are based primarily on the need for supplemental oxygen that

is used as a surrogate of the severity of the pulmonary damage. Supplemental oxygen is an important part in the management of these infants but in addition, it is implicated in the pathogenesis of BPD. Because there is no clear evidence on what the optimal arterial oxygen levels for these infants are, the indications for supplemental oxygen vary significantly from center to center. In addition, the need for supplemental oxygen can be influenced by altitude, drugs such as steroids or respiratory stimulants, and by the use of other forms of respiratory support such as nasal CPAP or mechanical ventilation. The proposed criteria to define BPD suggested in a National Institutes of Health (NIH) sponsored workshop in 1979 included a continued oxygen dependency *during the first 28 days* plus compatible clinical and radiographic changes (Bancalari et al. 1979). While these criteria were appropriate for the classic presentation of BPD, most infants today have intervals during the first days after birth when they do not require supplemental oxygen. Therefore, this criterion is not appropriate for the “New BPD.” To address this issue, some authors and clinicians have simplified this criterion and diagnose BPD in infants who are oxygen dependent “at” day 28. Although this simplified approach may work in most cases, it is possible that some infants who do not have significant lung disease may require supplemental oxygen only around day 28 because of acute conditions. This results in the erroneous labeling of those infants as BPD when in reality they do not have chronic lung damage. It is also possible that a premature infant may be on room air on day 28 and subsequently develop chronic lung damage and prolonged oxygen dependency. In order to avoid these problems, it is essential to include other indicators such as persistent radiographic changes and a minimal duration of oxygen therapy to reflect the chronicity of pulmonary damage.

The variation in the incidence of BPD when the different diagnostic criteria are applied to the same population of premature infants is illustrated in Fig. 48.1. Approximately one half of the infants who require oxygen *at* day 28 or for more than 28 days have a need for oxygen that persists to 36

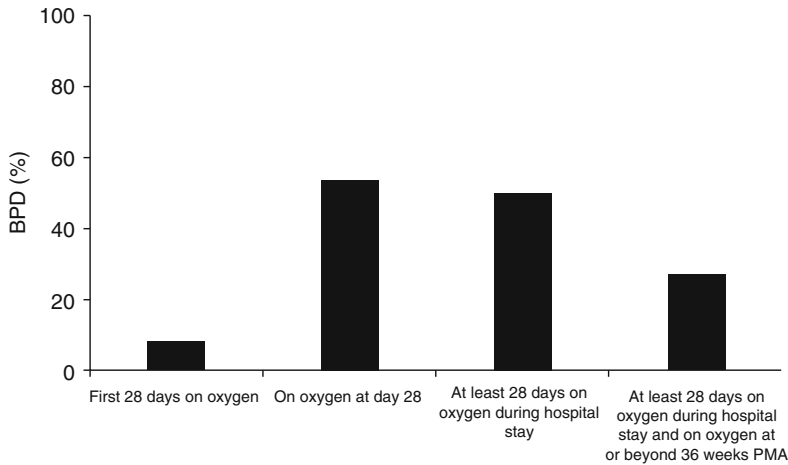


Fig. 48.1 Incidence of BPD using different definitions. Very few infants require oxygen continuously during the first 28 days after birth. In contrast, large proportions need oxygen at day 28 and for at least 28 days during their hospitalization. Only half of the latter group have a

persistent need for oxygen at or beyond 36 weeks PMA (Data from 673 infants born at JMH, years 2004–2008; gestational age, 23–30 weeks; and alive at 36 weeks PMA)

weeks postmenstrual age (36 weeks PMA). Only a small fraction of infants from this cohort have an uninterrupted need for oxygen during the first 4 weeks. This accounts for the very low BPD incidence when using this definition. Although small in number, most infants who continuously require oxygen during the first 28 days go on to become oxygen dependent at 36 weeks PMA, very much like in the classic form of BPD. These infants, however, account only for a minority of infants who develop BPD today. Presently, most infants born ≤ 30 weeks of gestation do not have continuous oxygen need during the first month of life but still many of them go on to develop BPD. This presentation accounts for most of the BPD cases today.

In order to circumvent some of these problems, and to focus on the more severely afflicted infants, it has been proposed to use the need for supplemental oxygen at 36 weeks PMA as a better criterion for BPD (Shennan et al. 1988). Because this is a stricter criterion than the 28 days oxygen supplementation, it identifies a group of infants with more severe lung damage and therefore better predicts poor long-term outcome. The criterion of oxygen dependency at 36 weeks PMA requires for an infant born at 24

weeks of gestation to be on oxygen for 12 weeks, while an infant born at 32 weeks of gestation would be labeled as BPD if he or she requires oxygen for only 4 weeks after birth.

Figure 48.2 shows the incidence of BPD among infants born at Jackson Memorial Hospital (JMH) within different birth weight and gestational age strata according to the criteria of oxygen dependency for ≥ 28 days in combination with oxygen need at 36 weeks PMA.

In order to address the inconsistencies in the diagnostic criteria of BPD and to come up with a better definition a workshop was organized by the NIH in 2000 (Jobe and Bancalari 2001). As a result of this effort, the recommendation was to use oxygen need for ≥ 28 days and at 36 weeks PMA to identify different severity of BPD and also to use the oxygen concentration at 36 weeks PMA to further define the severity of lung injury. It was also agreed that a minimum of 28 days of supplemental oxygen was necessary to make the diagnosis of BPD (Table 48.1). These recommendations solve many of the problems with previous criteria but it still has the limitations of using 36 weeks PMA that were discussed earlier.

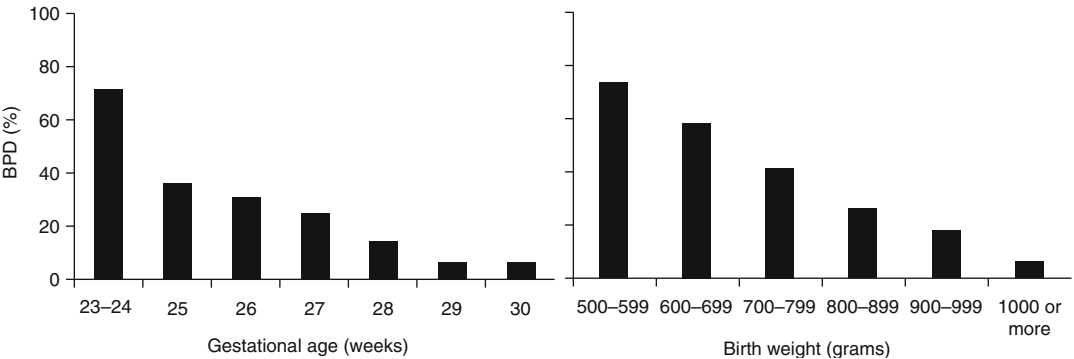


Fig. 48.2 Incidence of BPD by gestational age and birth weight. BPD defined as oxygen need for ≥ 28 days and at or beyond 36 weeks PMA (Data from 673 infants born at JMH during years 2004–2008; gestational age, 23–30 weeks; and alive at 36 weeks PMA)

Table 48.1 NIH consensus definition of BPD

Gestational age	<32 weeks	≥ 32 weeks
Time point of assessment	36 weeks PMA or discharge to home, whichever comes first	>28 days but <56 days postnatal age or discharge to home, whichever comes first
Treatment with oxygen >21 % for at least 28 days plus		
Mild BPD	Breathing room air at 36 weeks PMA or discharge, whichever comes first	Breathing room air by 56 days postnatal age or discharge, whichever comes first
Moderate BPD	Need ^a for <30 % at 36 weeks PMA or discharge, whichever comes first	Need ^a for <30 % at 56 days postnatal age or discharge, whichever comes first
Severe BPD	Need ^a for ≥ 30 % oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks PMA or discharge, whichever comes first	Need ^a for ≥ 30 % oxygen and/or positive pressure (PPV or NCPAP) at 56 days postnatal age or discharge, whichever comes first

Adapted from Jobe and Bancalari (2001)

BPD usually develops in neonates being treated with oxygen and positive-pressure ventilation for respiratory failure, most commonly respiratory distress syndrome

Persistence of clinical features of respiratory disease (tachypnea, retractions, rales) is considered common to the broad description of BPD and has not been included in the diagnostic criteria describing the severity of BPD. Infants treated with oxygen >21 % and/or positive pressure for non-respiratory disease (e.g., central apnea or diaphragmatic paralysis) do not have BPD unless they also develop parenchymal lung disease and exhibit clinical features of respiratory distress. A day of treatment with oxygen >21 % means that the infant received oxygen >21 % for more than 12 h on that day. Treatment with oxygen >21 % and/or positive pressure at 36 weeks PMA, or at 56 days postnatal age or discharge, should not reflect an “acute” event but should rather reflect the infant’s usual daily therapy for several days preceding and following 36 weeks PMA, 56 days postnatal age, or discharge

Definition of abbreviations: BPD bronchopulmonary dysplasia, NCPAP nasal continuous positive airway pressure, PMA postmenstrual age, PPV positive-pressure ventilation

^aA physiologic test confirming that the oxygen requirement at the assessment time point remains to be defined. This assessment may include a pulse oximetry saturation range

An important factor that is often ignored in the literature is the detailed and clear description of the base population in which the incidence of BPD is being reported. For example, reports that include only ventilated infants would have a higher rate of BPD than studies that include all live-born infants. Therefore, calculations of risk reduction and number needed to treat cannot be

extended to the general population of infants even within the same range of birth weight or gestation. Benchmarking comparisons should also account for differences in the base population in regard to mortality. The reported incidence per total admissions may be much lower than the incidence among premature infant surviving the neonatal period, at 36 weeks PMA or

at discharge. Inaccurate estimation of GA can also affect the calculated BPD incidence in a population where a consistent over- or underestimation of GA occurs.

Data combining results from competing outcomes are frequently found in the literature. For example, BPD or death, or survival without BPD is frequently reported as a combined outcome. This is done because BPD cannot be diagnosed in infants who die before the time point when diagnosis is made but it is essential that the outcomes are also reported separately. Regardless of the beneficial effect of a given intervention to prevent BPD, an increase in mortality or other serious complication beyond what is expected would nullify its use.

48.1.2.1 Prediction of Outcome

One of the main objectives of a diagnostic criterion for BPD is to predict the long-term pulmonary and neurodevelopmental outcome of preterm infants. The predictive value of the oxygen for ≥ 28 days, oxygen at 36 weeks PMA, and the NIH consensus definition was evaluated in a large cohort of infants from the National Institute of Child Health and Human Development (NICHD) neonatal network at 18–22 months corrected age (Ehrenkranz et al. 2005). The more liberal 28 days of oxygen criterion is more sensitive in detecting post-discharge respiratory complications but has poor specificity. Stricter definitions that use oxygen dependency at 36 weeks PMA and the more severe cases of need for $\geq 30\%$ oxygen are clearly more specific but at a cost of not classifying as BPD some infants that may later need additional respiratory care. These findings are similar to those reported from data obtained in the Trial of Indomethacin Prophylaxis in Preterms (TIPP) where oxygen need after day 28 was shown to be a more sensitive test (although less specific) than oxygen beyond 36 weeks PMA in predicting poor long-term pulmonary outcome (Davis et al. 2002). These results emphasize the importance of considering the respiratory evolution during the neonatal period in addition to the need for supplemental oxygen at a given point.

The BPD definition of oxygen at 36 weeks PMA is slightly more sensitive in predicting

mental and psychomotor developmental impairment but the definition of severe BPD (oxygen $\geq 30\%$ at 36 weeks PMA) increases the predictive sensitivity. A recent multivariate analysis indicated an increased risk of poor neurologic outcome among infants deemed to have BPD based on their oxygen need at 36 weeks PMA (Schmidt et al. 2003). Interpretation of these findings however is difficult because of the confounding effects of some risk factors for BPD as they may also be independently associated with poor neurologic outcome.

48.1.2.2 Physiologic Definition

In order to reduce the influence of different strategies for oxygen supplementation on the reported incidence of BPD (Ellsbury et al. 2002), Walsh and collaborators have devised a physiologic test to standardize the need for oxygen at the time when BPD is being diagnosed (Walsh et al. 2004). To accomplish this, infants with moderate dependency on oxygen at 36 weeks PMA ($<30\%$ oxygen) are challenged with room air breathing following a set weaning protocol to determine whether the supplemental oxygen is in fact needed. Although this test was applied in only 14 % of their entire cohort, it reduced the incidence of BPD from 35 to 25 % compared to the clinically prescribed oxygen supplementation. The use of this test clearly demonstrated that part of the reported variation in incidence of BPD among centers participating in the NICHD neonatal network was due to differences in clinical practice with respect to oxygen therapy. While the overall reduction in BPD incidence was 10 %, it ranged from 0 to 44 % in different centers demonstrating the wide variation in the use of supplemental oxygen. Over 40 % of the infants tested passed the challenge test and did not need the clinically prescribed oxygen.

Application of any diagnostic criteria also needs to consider other forms of respiratory support such as CPAP or IPPV. These interventions are included in the NIH consensus definition and can significantly influence the results of a diagnostic assessment and its relevance on outcome. However, they are rarely considered in the literature. Most definitions of BPD use supplemental

oxygen as the main parameter to define chronic lung damage. This is associated with a number of limitations. Whether a small preterm infant remains on supplemental oxygen for 28 days or until 36 weeks PMA may not be very important because most of these infants remain hospitalized past the 36 weeks PMA for reasons other than their oxygen requirement. Therefore, the duration of oxygen therapy is not very important unless it predicts poor long-term outcome. Unfortunately, the reported predictive value of oxygen need in terms of long-term outcome has not been very strong.

48.1.3 General Management of the Infant with BPD

The management of the infant with BPD is aimed at preserving adequate gas exchange and at the same time preventing the progression of the disease by reducing factors that predispose to lung damage. The difficulty in the management of these infants is that many of the therapies used to maintain gas exchange such as supplemental oxygen and mechanical ventilation are major contributors in the pathogenesis of this disease.

48.1.3.1 Fluid Management and Diuretics

Infants with BPD frequently accumulate excessive fluid in their lungs and tolerate even normal amounts of fluid intake poorly. The pulmonary edema contributes to the respiratory failure and ventilator dependency. For this reason, water and salt intake should be limited to the minimum required to provide the necessary calories for their metabolic needs. When evidence of pulmonary edema persists despite fluid restriction, diuretic therapy can be used. The use of diuretics in infants with BPD can be associated with an improvement in lung compliance and decrease in resistance, but the effect on gas exchange is less consistent. Chronic diuretic therapy can be associated with serious side effects that include hypokalemia, hyponatremia, metabolic alkalosis, hypercalciuria with nephrocalcinosis, hypochloremia, and hearing loss. Some of these side

effects may be reduced by using an alternate-day therapy with furosemide.

Because of the side effects and the lack of evidence that prolonged use of diuretics changes the long-term outcome in infants with BPD (Kao et al. 1994), this therapy should be left only for acute episodes of deterioration associated with evidence of pulmonary edema. Distal tubular diuretics such as thiazides and spironolactones are also used in infants with BPD but the improvement in lung function with these diuretics is less consistent than with proximal loop diuretics. However, the side effects such as nephrocalcinosis and hearing loss may be less prevalent than with furosemide and for this reason, these diuretics are used in infants with established BPD who receive diuretic therapy for prolonged periods of time.

48.1.3.2 Bronchodilators

Infants with severe BPD may have airway smooth muscle hypertrophy and airway hyperreactivity. Hypoxia can increase airway resistance in these patients, and therefore, maintenance of adequate oxygenation is important to avoid bronchoconstriction. Inhaled bronchodilators including β agonists, such as isoproterenol, salbutamol, metaproterenol, and isoetharine, and anticholinergic agents, such as atropine and ipratropium bromide, have been used to reduce airway resistance in infants with BPD. Their effect is usually short-lived and many of these drugs have cardiovascular side effects such as tachycardia, hypertension, and possible arrhythmias so they should be used with caution and only when indicated.

Methylxanthines (aminophylline and caffeine) also have been shown to reduce airway resistance in these infants. These drugs have other potential beneficial effects, such as respiratory stimulation and mild diuretic effect, and aminophylline may also improve respiratory muscle contractility. These drugs must also be used with caution because of their multiple side effects.

There is no evidence that prolonged use of bronchodilators changes the course of infants with BPD and for this reason it is advisable to limit their use to episodes of acute exacerbation of airway obstruction.

48.1.3.3 Anti-inflammatory Drugs/ Corticosteroids

Inflammation is an important factor in the pathogenesis of BPD, and therefore, anti-inflammatory agents have been used during the early stages of the disease to ameliorate its progression. Several studies have shown rapid improvement in lung function after the administration of steroids, facilitating weaning from the ventilator and a reduction in BPD incidence when compared with controls who received placebo. The possible mechanisms for the beneficial effect of steroids include enhanced production of surfactant and antioxidant enzymes, decreased bronchospasm, decreased pulmonary and bronchial edema and fibrosis, improved vitamin A status, and decreased responses of inflammatory cells and mediators in the injured lung. Potential complications of prolonged steroid therapy include masking the signs of infection, arterial hypertension, hyperglycemia, increased proteolysis, adrenocortical suppression, somatic and lung growth suppression, and hypertrophic cardiomyopathy. In addition, long-term follow-up studies suggest that infants who received early or prolonged steroid therapy have worse neurologic outcome, including an increased incidence of cerebral palsy (Committee on Fetus and Newborn 2002; O'Shea et al. 1999; Yeh et al. 1998). Because of the seriousness of these complications, specifically when systemic steroids are used early after birth, and until more information on safety is available, it is recommended to use systemic steroids after the first 2 weeks of life and only in infants who show evidence of severe and progressive pulmonary damage and remain oxygen and ventilator dependent. The dose and duration of therapy should be limited to the minimum necessary to achieve the desired effects, usually 4–7 days and the potential side effects should be discussed with the family.

Steroids have also been administered by nebulization to minimize the systemic side effects, but data on effectiveness and side effects are not conclusive enough to recommend their routine use (Cole et al. 1999; Groneck et al. 1999).

48.1.3.4 Pulmonary Vasodilators

Pulmonary hypertension is a common and serious complication in infants with severe BPD. Because pulmonary vascular resistance is extremely sensitive to changes in alveolar PO_2 , it is important to maintain normal oxygenation at all times.

In infants with severe pulmonary hypertension and cor pulmonale, the calcium channel blocker nifedipine has been shown to decrease pulmonary vascular resistance but this drug is also a systemic vasodilator and can produce a depression of myocardial contractility. Its safety and long-term efficacy in these infants has not been established.

Inhaled nitric oxide is also administered to infants with BPD in an attempt to improve ventilation-perfusion matching, reduce pulmonary vascular resistance, and reduce inflammation. Although NO has been shown to improve oxygenation (Banks et al. 1999), there is no clear evidence that this therapy improves long-term outcome, hence should still be considered experimental. Phosphodiesterase inhibitors (sildenafil), prostacyclin (epoprostenol), and ET-1 antagonists are potent pulmonary vasodilators that have been used to treat pulmonary hypertension but there is not enough information on their safety and efficacy to recommend their routine use in infants with BPD.

48.1.3.5 Nutrition

Adequate nutrition is an important aspect of care for the infant with BPD. Malnutrition can delay the development of new alveoli and can decrease muscle strength, making successful weaning from mechanical ventilation more difficult. Malnutrition can also make infants more prone to infection and oxygen toxicity. High-calorie formulas and supplements of protein, calcium, phosphorus, and zinc are used to maximize the intake of calories while restricting fluid intake to prevent congestive heart failure and pulmonary edema (Brunton et al. 1998). When enteral nutrition is not possible, parenteral alimentation must be used until the gastrointestinal tract again becomes functional. Bone demineralization is frequently observed in infants with BPD as a

manifestation of rickets secondary to deficiency of calcium or vitamin D and excessive calciuria resulting from chronic diuretic therapy. Administration of extra calcium and vitamin D is necessary to prevent rickets in these infants. Infants who receive exclusively parenteral nutrition for prolonged periods are more susceptible to developing deficiency of specific nutrients, such as vitamins A and E, and trace elements, such as iron, copper, zinc, and selenium, all of which play a role in antioxidant function, protection against infection, and lung repair. Decreased caloric intake potentiates oxygen-induced lung damage and interferes with cell multiplication and lung growth. Deficiency of sulfur-containing amino acids may also affect lung levels of glutathione, a potent antioxidant. Infants with severe BPD have been shown to have lower plasma levels of vitamin A and a deficiency of this vitamin in experimental animals results in loss of ciliated epithelium and squamous metaplasia in the airways, changes similar to those observed in severe BPD. Clinical studies in preterm infants with prolonged respiratory failure suggest that maintenance of normal plasma levels of vitamin A reduces the incidence and severity of BPD (Shenai 1999; Shenai et al. 1987; Tyson et al. 1999). The use of supplemental vitamin A by intramuscular injection to maintain normal serum levels is effective, but its use is not widespread because of the relatively small effect on BPD and the reluctance to give repeated intramuscular injections to very small infants.

Gastroesophageal reflux is common in infants with BPD and it may contribute to malnutrition and lung damage. When severe reflux is documented, aggressive anti-reflux management, including surgery, may be indicated to alleviate the respiratory symptoms.

48.1.4 Respiratory Care in the Infant with BPD

48.1.4.1 Oxygen Therapy

While it is important to reduce the use of oxygen as much as possible to avoid toxicity, it is also important to ensure adequate tissue oxygenation

and to avoid the pulmonary hypertension and cor pulmonale that can result from chronic hypoxemia. There is no conclusive information to recommend a specific range of oxygen saturation in these infants, but there is clear evidence that oxygen saturations above 95 % and PaO₂ above 70 mmHg are associated with higher incidence of ROP and worse respiratory outcome (Askie et al. 2003; Bancalari et al. 1987; Tin 2004). Because of this, it is recommended to maintain the saturations between 90 and 95 % and the PaO₂ between 50 and 70 mmHg to minimize the detrimental effects of hypo- and hyperoxemia. In many cases, oxygen therapy is required for several months or even years and many of these patients are discharged with oxygen therapy at home.

Adequacy of gas exchange is monitored by determining arterial blood gas levels at intervals dictated by the child's clinical condition. Blood gas determinations obtained by arterial puncture may not be reliable because the infant usually responds to pain with crying or apnea. Transcutaneous PO₂ electrodes are also inaccurate in these infants because they frequently underestimate the true PaO₂. Pulse oximeters offer the most reliable estimate of arterial oxygenation and have the advantage of simplicity of usage and the possibility of assessing continuous oxygenation.

Because of the increased metabolic demands in infants with BPD, associated in severe cases with low arterial oxygen tension, it is important to maintain a relatively normal blood hemoglobin concentration.

48.1.4.2 Mechanical Ventilation

Mechanical ventilation is one of the main factors associated with the pathogenesis of BPD, and therefore, it is essential to use the lower settings necessary to maintain gas exchange and reduce the duration of mechanical support to a minimum. In order to minimize overdistension and injury the peak airway pressure should be the minimal necessary to obtain adequate tidal volumes. Inspiratory times between 0.3 to 0.5 s with flow rates between 5 and 10 l/min are used because shorter inspiratory times and higher flow rates may exaggerate the maldistribution of the

inspired gas. Longer inspiratory times may increase the risk of overdistension and alveolar rupture and negative cardiovascular side effects. End-expiratory pressure is adjusted between 4 and 8 cm H₂O to maintain lung volume so that the minimum oxygen concentration necessary to keep oxygen saturation above 90 % (PaO₂ above 50 mmHg) is used. In infants with severe airway obstruction, especially those with bronchomalacia, the use of higher PEEP levels of up to 10 cm H₂O may be necessary to avoid expiratory airway collapse and preserve alveolar ventilation. The duration of mechanical ventilation must be limited as much as possible to reduce the risk of further ventilator-induced lung injury and infection. Weaning these patients from mechanical ventilation is very difficult and must be accomplished gradually. When the patient is able to maintain an acceptable PaO₂ and PaCO₂ with low peak inspiratory pressures (lower than 15–20 cm H₂O) and a FiO₂ lower than 0.3–0.4, the ventilator rate is gradually reduced to allow the infant to perform an increasing proportion of the respiratory work. The use of patient-triggered ventilation and pressure support of the spontaneous breaths can accelerate the process of weaning and reduce the total duration of mechanical ventilation (Greenough 2001; Reyes et al. 2006).

During the weaning process, the need to increase the FiO₂ to maintain oxygen saturation within an acceptable range is common. The PaCO₂ may also rise to values in the 50–60 mmHg or higher. As long as the pH is within acceptable limits, certain degree of hypercapnia must be tolerated in order to wean these patients from the ventilator. In small infants with poor central respiratory activity, respiratory stimulants such as aminophylline or caffeine are used during the weaning phase. When the patient is able to maintain acceptable blood gas levels for several hours on low ventilator rate (10–15 breaths/min), extubation can be attempted. During the days that follow extubation, it is important to provide chest physiotherapy to prevent airway obstruction and lung collapse caused by retained secretions. In smaller infants with poor respiratory drive and frequent apneic episodes, the use of nasal CPAP or nasal IMV can stabilize respiratory function and reduce

the need for reinstitution of mechanical ventilation. Despite all these steps to facilitate weaning, it is not uncommon that small infants fail extubation and need to be placed back on mechanical ventilation. In infants with severe BPD it sometimes becomes necessary to perform a tracheostomy to facilitate their respiratory care and be able to wean them from mechanical ventilation.

Essentials to Remember

- The severe forms of BPD seen before are relatively uncommon today. Instead many premature infants present with milder forms of BPD that result from a different multifactorial pathogenic process.
- Definitions of BPD are primarily aimed at standardizing terminology and providing a prognostic insight into the respiratory condition in childhood. Use of standardized definitions is key for intra- and inter-center benchmarking purposes.
- Strategies used in the care of infants with BPD should focus in breaking the cycle of dependency for respiratory support and injury that results from this support.

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Educational Aims

- To understand the underlying pathophysiology of ALI in children as an inflammatory disease
- To learn the therapeutic/supportive measures and its limitations
- To learn that ALI in children has different aspects compared to ALI in adult patients
- To understand why it may be important to diagnose ALI on a daily routine in order to consider appropriate therapeutic management

American-European Consensus Criteria (AECC) for ALI (Table 49.1), of which approximately 80 % suffer from its most severe form, i.e., the acute respiratory distress syndrome (ARDS) (Bernard et al. 1994; Bindl et al. 2005; Dahlem et al. 2003). The AECC criteria aim to guide clinicians in their daily judgement of patients and also help researchers to define a homogenous group of patients for investigations.

49.1 Definition

Acute lung injury (ALI) is characterized by acute pulmonary inflammation causing severe hypoxia and often leading to respiratory failure. About 9 % of mechanically ventilated children admitted to a pediatric intensive care unit (PICU) fulfill the

49.2 Pathophysiology

ALI is triggered by a local injury or infection directly in the lung (direct injury) or by overwhelming systemic inflammation (indirect injury). In children, viral and bacterial pneumonia and systemic sepsis are most common triggering events (Dahlem et al. 2003; Flori et al. 2005;

Table 49.1 The American-European Consensus Conference definitions of ALI and ARDS (Bernard et al. 1994)

Onset		Acute
Oxygenation	ALI	$\text{PaO}_2/\text{FiO}_2 < 300$ (regardless of positive end-expiratory pressure level)
	ARDS	$\text{PaO}_2/\text{FiO}_2 < 200$ (regardless of positive end-expiratory pressure level)
Chest radiograph		Bilateral infiltration seen on frontal chest radiograph
Pulmonary artery occlusion pressure		< 18 mmHg when measured or no clinical evidence of left atrial hypertension

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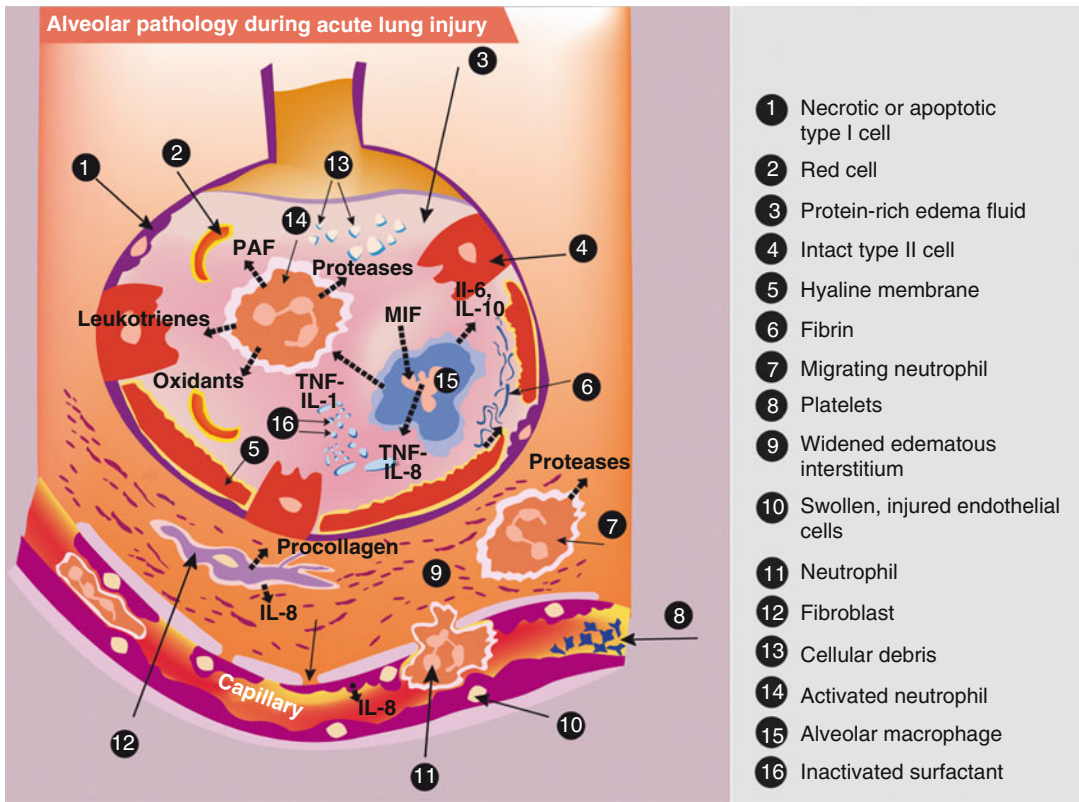


Fig. 49.1 Illustration of the acute phase of acute lung injury (ALI). In the acute phase of ALI, there is formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils travel through the interstitium into the air space. Alveolar macrophages secrete interleukin-1, interleukin-6, interleukin-8, and interleukin-10, as well as tumor necrosis factor alpha (*TNF- α*)

which stimulate and activate neutrophils. Neutrophils release pro-inflammatory molecules (oxidants, proteases, leukotrienes, platelet-activating factor (PAF)). The influx of protein-rich edema fluid into the alveolus has led to the inactivation of surfactant and, together with unresolved fibrin deposition, fibrin-rich hyaline membranes are formed (Adapted from Dahlem et al. (2007))

Hammer et al. 1997). Other triggers for direct lung injury are aspiration of gastric contents, foreign bodies, or toxic agents such as hydrocarbons, smoke inhalation, near-drowning events, and pulmonary contusion. Indirect triggers of ALI include pancreatitis, systemic burn injury, and major trauma. After the initial injury, cell-mediated mechanisms cause a variety of reactions such as mediator release, activation of polymorphonuclear neutrophils, and initiation of the coagulation cascade. Alveolar-capillary cell damage and disturbance of the alveolar-capillary membrane cause high-permeability edema with flooding of the alveolar space and inactivation of surfactant (Bachofen and Weibel 1977, 1982).

In general, resolution occurs soon after the underlying disease (e.g., sepsis) is successfully treated. Usually within the second week of illness, inflammation ceases, alveolar-capillary function restores, surfactant production restarts, water clearance in lung tissue occurs, and, thus, lung compliance and gas exchange improve (Bernard et al. 1994; Marshall et al. 2000; Ware and Matthay 2000). Resolution of ALI is hampered in a proportion of patients. Histologically, they show pulmonary fibrosis with permanent loss of lung tissue and lung compliance (Bitterman 1992; Ingbar 2000; Shimabukuro et al. 2003). Figures 49.1 and 49.2 summarize the current understanding of the inflammatory scenario (Dahlem et al. 2007).

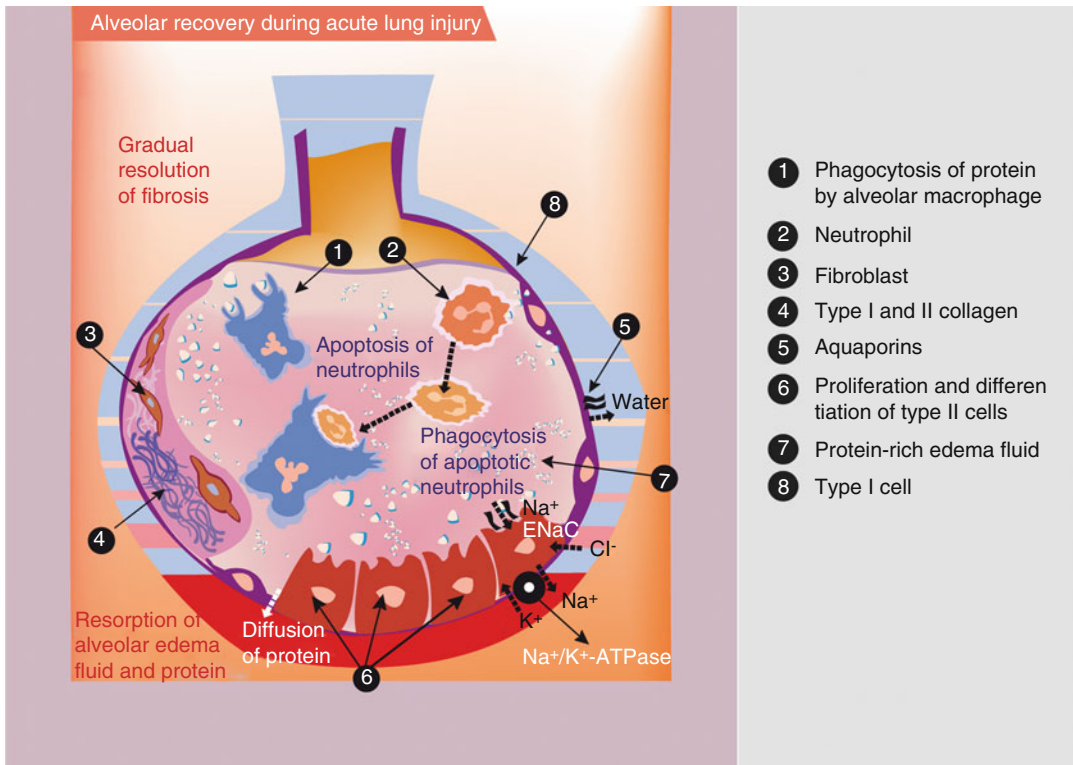


Fig. 49.2 Illustration of the recovery from acute lung injury. During recovery de novo proliferation and differentiation of alveolar type II cells occurs (on the *right-hand side* of the figure). For complete resolution, it is important that water is moving via additional aquaporines and by recovery of sodium and chloride channel function (ENaC) and sodium pump (Na⁺/K⁺-ATPase). Also intra-

alveolar protein must be cleared by paracellular diffusion and secondarily by endocytosis. Furthermore, insoluble debris (protein, apoptotic neutrophils) is removed by macrophages. The gradual remodeling and resolution of intra-alveolar and interstitial granulation tissue and fibrosis are very important for complete recovery (*left-hand side* of the figure) (Adapted from Dahlem et al. (2007))

49.3 Lung Mechanics

From the first anatomical and functional characterizations of ARDS in adult patients until the present, ALI is recognized as a restrictive lung disease. Lung compliance is reduced due to accumulation of interstitial and alveolar plasma leakage, inactivation of surfactant, and alveolar collapse (Gunther et al. 1996; Petty and Ashbaugh 1971). These alterations are distributed inhomogeneously in all lung regions with a preponderance of dependent lung regions (Gattinoni et al. 1986). Distinct respiratory function testing in children with ALI confirms the restrictive abnormalities in lung mechanics in this age group (Newth et al. 1997). As a routine bedside assessment, an X-ray can visualize bilateral new infiltrates (Fig. 49.3) (Dahlem et al. 2007).

49.4 Epidemiology

Population-based studies revealed a prevalence of ALI in children that is between 2 and 16 per 100,000 person-years with an age-related increase (Bindl et al. 2005; Erickson et al. 2007). Mortality ranges between 18 and 27 % accounting, e.g., for up to 2,000 deaths per year in the USA (Dahlem et al. 2003; Flori et al. 2005; Peters et al. 1998; Randolph 2009). Boys are more prone to develop ALI than girls (Bindl et al. 2003). It appears that differences in lung mechanics and lung volume between the sexes might be responsible for this observation (Stocks et al. 1997). The exact mechanisms of this observation require further exploration.

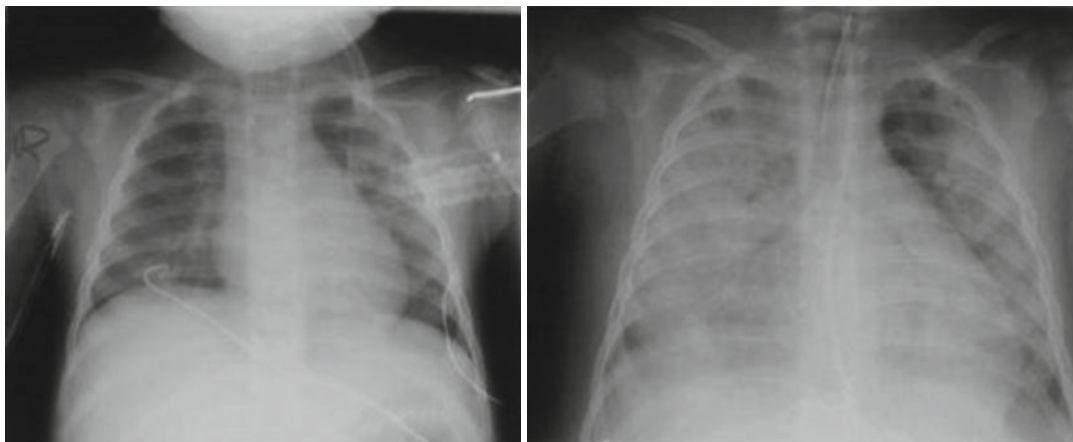


Fig. 49.3 A child with meningococcal septic shock and acute lung injury. Day 1 of ICU admission: the *left-hand image* shows bilateral infiltrates. Day 3 of ICU admission:

the *right-hand image* shows progression to generalized infiltrates with pleural effusions (Adapted from Dahlem et al. (2007))

49.5 Risk Factors

Five pediatric studies on the epidemiology of ALI have shown a correlation between the severity of hypoxia and mortality (Costil et al. 1995; Dahlem et al. 2003; Erickson et al. 2007; Flori et al. 2005; Goh et al. 1998). Commonly used markers of hypoxia such as the ratio of partial arterial oxygen pressure to fraction of inspired oxygen (P/F ratio) and the oxygenation index ((mean airway pressure $\times$ and fraction of inspired oxygen)/partial arterial oxygen pressure) are predictive of mortality. In four of these studies, the presence of multiple organ failure also showed a trend towards higher mortality in these children (Dahlem et al. 2003; Erickson et al. 2007; Flori et al. 2005; Goh et al. 1998).

49.6 Clinical Relevant Outcomes in Trials

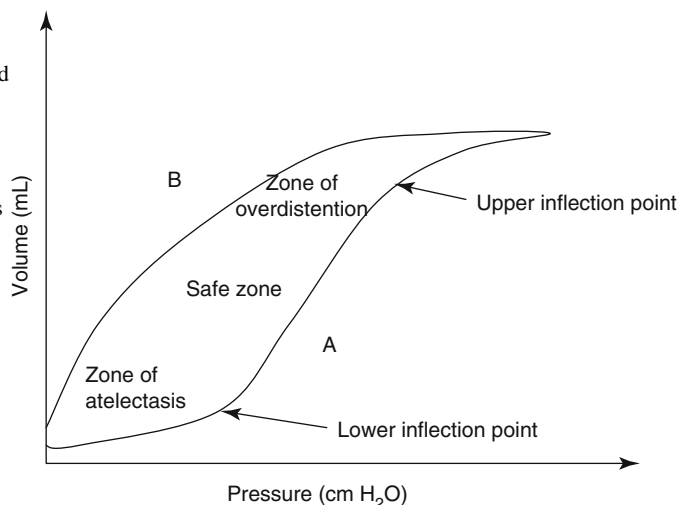
Mortality is considered the most relevant primary end point for clinical trials investigating life-threatening disorders. Because of the low mortality in pediatric ALI, 2,000 children would be required in each ALI study arm to detect a moderate (25 %) decrease in mortality ($\alpha=0.05$, $\beta=0.80$) (Randolph 2009). Because this is not feasible, non-mortality outcome measures are needed for clinical trials in ALI. Ventilator-free

days (VFDs), respiratory function tests, cognitive deficits, and estimates of the quality of life might be acceptable end points due to their importance for health care economics and for the developing child (Ben Abraham et al. 2002; Dahlem et al. 2004a; Knoester et al. 2007; Schoenfeld and Bernard 2002).

49.7 Clinical Management of Acute Hypoxic Respiratory Failure

Due to hypoxia, children with ALI should receive oxygen supplementation immediately via a face mask. Additionally, the underlying disease (e.g., sepsis) should be treated vigorously and the general condition of the child should be stabilized by supportive therapy following the rules of intensive care therapy. With respect to respiratory failure, anatomic and physiological considerations in young children should be addressed. Children have smaller airways with higher airway resistance, lower functional residual capacity (FRC), and more rigid chest wall than adults. These characteristics in anatomy and lung mechanics put children with ALI at higher risk of severe hypoxic respiratory failure (Newth et al. 1997). Furthermore, 80 % of children with ALI develop hypoxic respiratory failure deteriorating rapidly within the first 48 h to the severe category of

Fig. 49.4 The hysteresis of the pressure-volume curve of the lung. A inflation limb; B deflation limb. On inflation (A) lungs need higher pressures to inflate than on deflation. On deflation (B), the higher lung volume can be maintained on lower pressure. Thus, once the lung is open, it is more compliant. At the lower inflection point, the lung opens up, compliance improves, and, at the upper inflection point, optimal lung volume is achieved. At overinflation, compliance decreases and lung injury occurs (Adapted from Dahlem et al. (2007))



this syndrome, ARDS (Dahlem et al. 2003). Therefore, and not surprisingly, most children with ALI need mechanical ventilation (MV) during the course of the disease. In one study, it was shown that although a substantial fraction of children (28 %) did not require mechanical ventilation at the onset, 46 % of these patients eventually required MV for worsening ALI (Flori et al. 2005) .

Disappointingly, no precise guidelines exist regarding initialization of MV except in situations with loss of consciousness or the need for airway protection. Depending on the underlying disease and the child's general condition (e.g., decreased mental status, exhaustion due to high workload of breathing), clinicians should be ready at all times to institute mechanical ventilation while closely monitoring of vital parameters. Finally, appropriate MV can provide adequate ventilation volumes for clearance of CO₂ and restoring FRC for oxygenation.

Before initializing MV and choosing appropriate ventilator settings, intensive care physicians in particular are obliged to ensure that they are optimizing the benefit of the therapy and minimizing the risk of inflicting secondary harm (Hippocratic Oath, Greek: ἐπὶ δηλῆσαι δὲ καὶ ἀδικίῃ εἰρᾶναι). Against this background and the knowledge of deleterious complications during the early years of MV, investigations focused on the dark side of MV. Convincing evidence has accrued over the last three decades that MV – despite the potential

benefits and life-saving aspects – can damage the lungs and can kill patients (Kumar et al. 1973). What is now called ventilator-induced lung injury (VILI) shows similar histopathological and biochemical alterations as original ALI (American Thoracic Society, The European Society of Intensive Care Medicine, and The Societe de Reanimation de Langue Francaise 1999; Slutsky 2005).

The lungs are damaged by shear forces created by ventilation with high VT (volutrauma) in situations where alveolar collapse (atelectrauma) occurs after each respiratory breath. In combination with ALI, VILI aggravates the clinical course and increases mortality of ALI patients. Many experimental studies with lung injury models have shown that ventilator settings should be chosen to keep the lung open (atelectrauma) and to avoid high tidal volumes. Theoretically, this can be achieved by institution of ventilation within a safe – i.e., the most compliant – zone of the pressure-volume curve (Fig. 49.4) (American Thoracic Society, The European Society of Intensive Care Medicine, and The Societe de Reanimation de Langue Francaise 1999; Slutsky 2005). Identifying this safe zone in actual practice is more difficult. Despite some controversy, clinical and experimental studies suggest that in patients with severe ARDS, lung-protective ventilation is established by sufficient positive end-expiratory pressure (PEEP), plateau pressure below 30 cm H₂O, and tidal volume (Vt) below

6 mL/kg (The Acute Respiratory Distress Syndrome Network 2000; Hager et al. 2005; Petrucci and Iacovelli 2007). FiO_2 should be kept as low as possible to achieve adequate SpO_2 and titrated according to a systematic approach with PEEP to avoid oxygen toxicity. In the ARDS-network trial, adult patients with ARDS showed improved survival with this ventilation strategy. Controlled clinical studies to reproduce these results in children were regarded as not feasible due to the low incidence and mortality of pediatric ALI (Hanson and Flori 2006). Alternatively, comparison with historical controls has shown that the implementation of the high PEEP and low V_t approach already changed ventilation practice on PICUs and might be responsible for the improvement of outcomes during the past two decades (Albuali et al. 2007; Miller and Sagy 2008). Although not designed to examine ventilation strategy, a pediatric ALI study investigating the effects of prone position during MV also applied lung-protective ventilator settings. In the control group with an average V_t not higher than 7 mL/kg and an average PEEP between 7 and 10 cmH_2O , the lowest mortality rate yet of only 8 % was reported (Curley et al. 2005).

Alternatively to conventional pressure ventilation, high-frequency oscillatory ventilation (HFOV) is thought to be the ideal ventilation technique in patients with ALI. HFOV should prevent VILI by reducing V_t to a minimum of dead-space volume and by a continuous distending pressure guaranteeing FRC. Despite positive experiences of single centers, controlled data of a single randomized controlled trial (RCT) showed only improvement in oxygenation but no improvement in survival (Arnold et al. 1994, 2000).

Mechanical ventilation in children requires endotracheal intubation by experienced and skilled personal. Thereby, cuffed tubes are safe and prevent air leakage due to volume loss especially in lungs with very low compliance and high ventilator settings (Clements et al. 2007). Endotracheal intubation, however, carries risks such as tube misplacement, injuries to the airway, the need for deep sedation, and pneumonia

(Page et al. 1998). Therefore, noninvasive ventilation methods gained increasing attention and were subjected to clinical trials in adult patients, with no conclusive evidence in favor of use. Recently, a Cochrane review examined the use of continuous negative extrathoracic pressure and continuous positive airway pressure ventilation as noninvasive modes of respiratory support. They found that there are no controlled studies in children on noninvasive modes of respiratory support available; therefore, no definite conclusions can be drawn on this topic at the moment (Shah et al. 2008).

Vital organs (brain, heart, liver, and kidney) are sensitive to hypoxia. However, oxygen mixed to the inspired gas is considered toxic with the potential hazards for organ damage (Capellier et al. 1999). Therefore, oxygen concentrations in arterial blood should be monitored closely by measuring percutaneous oxygen saturation (SpO_2) or arterial oxygen concentrations (PaO_2). To avoid aggressive ventilator settings, reasonable target values of SpO_2 88–95 % and PaO_2 55–88 torr or strategies accepting even lower values are routinely applied; however, these lack validation of potential harm to the developing brain. In this context, it has also been recommended to accept higher values of PaCO_2 and lower pH to keep plateau pressure and V_t as low as possible (Kavanagh and Laffey 2006). However, similarly, there are no appropriate outcome studies in children with ALI supporting these strategies.

Appropriate ventilator settings can preserve FRC. Computerized tomography studies of ARDS lungs examined dependent lung regions in dorsal parts of the lung during supine positioning (Gattinoni et al. 1986). Gravity and loss of compliance predispose to alveolar collapse. It was shown that by turning the patient around into prone position, these regions can be kept patent or reopened, thus improving lung mechanics and oxygenation (Pelosi et al. 2002). In children, these positive physiological effects have been confirmed (Numa et al. 1997). Disappointingly, and consistent with trials in adults with ALI, the largest RCT did not show

benefits in the most relevant outcome variables such as mortality or ventilator-free days (Casado-Flores et al. 2002).

49.8 Adjunctive Therapies

MV is only a supportive measure. Therapies should address the pathophysiological alterations in ALI. Hypoxia in ALI is caused by ventilation/perfusion mismatch with increased intrapulmonary shunting and imbalance in pulmonary blood flow. Selective pulmonary vasodilatation is, therefore, considered one promising therapeutic option. Inhaled nitric oxide (INO) and aerosolized prostacyclin (PGI₂) are commonly used therapeutics for this indication (Adhikari et al. 2007; Dahlem et al. 2007). In the only RCT in children with severe hypoxic respiratory failure including cases of ALI, INO improved hypoxia by at least 20 % (Dobyns et al. 1999). Inhaled PGI₂ showed similar physiological effects in one RCT (Dahlem et al. 2004b). However, both studies did not show positive effects on clinical relevant outcomes, although they were not designed to answer these questions.

Surfactant inactivation and disruption of production is one of the major consequences of pulmonary inflammation during ALI (Gunther et al. 1996). A first RCT of surfactant installation in children with ALI improved oxygenation and reduced mortality (Willson et al. 2005). Efficacy appears to depend on the cumulative dose and timing of application. The PALISI network (http://pedscm.org/PALISI_network.php) is now studying the effects of calfactant and lucinactant in children with ALI (Randolph 2009).

Another approach for a causative therapy is to slow down or inhibit the inflammatory alterations during ALI. Results from adult ALI/ARDS studies with corticosteroids raised more questions than gained answers. It seems that within a narrow (low dose) and a well-defined timing range (early in the course), corticosteroid therapy has the potential to improve outcome (Steinberg et al. 2006). To date, there has been no clinical trial of steroids for ALI in children.

49.9 Mechanical Ventilation Failure

In the absence of appropriate causative therapies and with the knowledge of the difficulties to design the best ventilator settings to prevent VILI, one should support the lungs until critical illness has abated. Extracorporeal membrane oxygenation (ECMO) has shown to bridge this period facilitating oxygenation and CO₂ removal in desperate situations of pediatric hypoxic respiratory failure and ALI (Goldman et al. 1997; Green et al. 1996). Parallel to the extensive requirements to install ECMO and the fact that it is not available on every PICU, most physicians regard ECMO as a rescue therapy for desperate cases. In these children with an expected mortality of almost 100 %, ECMO can save lives in approximately 50 % of such cases. Due to high costs, bleeding complications, and decreasing mortality in pediatric ALI, attempts to conduct a RCT led to early termination (Spear and Fackler 1998).

49.10 General Supportive Care

Children with ALI are critically ill as devastating underlying illness deregulates many crucial physiological processes leading to life-threatening abnormalities. The mainstay of supportive care in children with ALI is treatment on a well-equipped PICU with appropriate monitoring and respiratory machines and special trained nurses and physicians. Correction of the most important alterations is reasonable and occurs daily; however, no RCTs have yet shown cutoff values for therapies with regard to improving outcome (Dahlem et al. 2007; Randolph 2009; Randolph et al. 2003). One should also not disregard the hazards of overtreatment (Cochrane Injuries Group Albumin Reviewers 1998; Sanchez and Toy 2005). Despite the large gap in scientific data for evidence-based recommendations, the authors offer in Table 49.2 an overview of a practical approach to routine management.

Table 49.2 Recommendations for routine management of children with ALI beside routine critical management

Data to	Recommended guide use	Promising preliminary data	May be applied on individual trial basis	Option for rescue therapy
Keep plateau pressure ≤ 30 cm H ₂ O	A (The Acute Respiratory Distress Syndrome Network 2000), EO			
Avoid tidal volumes ≥ 10 mL/kg ^a	A (The Acute Respiratory Distress Syndrome Network 2000), EO			
4–6 mL/kg ^a tidal volume protocol		A (The Acute Respiratory Distress Syndrome Network 2000)		
PaO ₂ goal 60–80 torr (8–10.7 kPa) (SpO ₂ ≥ 90 %)	EO			
pH goal of 7.30–7.45	EO			
Prone positioning			P (Casado-Flores et al. 2002), EO	
Inhaled nitric oxide/prostacyclin				P (Adhikari et al. 2007; Dahlem et al. 2004b), EO
Corticosteroids for lung inflammation		A (Petrucchi and Iacovelli 2007)		
Noninvasive ventilation		P (Slutsky 2005)		
High-frequency oscillatory ventilation		P (Arnold et al. 1994)		
Endotracheal surfactant		P (Wosten-van Asperen et al. 2008)		
Hemoglobin target ≥ 10 g/dL, if unstable ^b	EO			
Hemoglobin target ≥ 7 g/dL, if not unstable ^b	P (Marshall et al. 2000), EO			
ECMO				P (Green et al. 1996), EO

Adapted from Rubenfeld et al. (2004)

A evidence from adult cohorts, P evidence from pediatric cohorts, EO expert opinion, ECMO extracorporeal membrane oxygenation

^aIdeal or adjusted body weight

^bUnstable, hemodynamic shock or profound hypoxia

49.11 Future Directions

Future research should identify children at risk for ALI early in the course or at admission in order to prevent development of ALI or at least deterioration to ARDS (Dahlem et al. 2003; Flori et al. 2005). Identifying novel gene candidates in this context which are associated with lung injury might be a promising new direction to

define patients at risk for ALI (Wosten-van Asperen et al. 2008). Angiotensin-converting enzyme (ACE) activity in bronchoalveolar lavage fluid (BALF) of mechanically ventilated rats triggers inflammation and apoptosis, and pretreatment with an ACE inhibitor reduces pulmonary inflammation and apoptosis (Wosten-van Asperen et al. 2008). Interestingly, a polymorphism in the gene-encoding ACE

increases the probability of death due to ARDS (Jerng et al. 2006, 2007).

New treatment options such as corticosteroids, surfactant, and lung-protective ventilation should be examined in relation to the underlying diseases. Special considerations should be directed to subgroups of ALI children. For example, in the calfactant study, surfactant improved outcome dramatically in the subgroup of immunocompromised children by lowering mortality to 50 % (Willson et al. 2005). Alveolar fibrin turnover is misbalanced towards an antifibrinolytic milieu with activation of the coagulation cascade. Therapeutic interventions may offer new options improving surfactant function and restoring the integrity of the alveolar-capillary membrane. In human volunteers, instillation of activated protein C into the lung inhibited coagulation activation by endotoxin (van der Poll et al. 2005).

There is a scarcity on follow-up data on pediatric ALI. Preliminary studies indicate that a relevant number of children will suffer from lifelong sequelae (e.g., health-related quality of life, neurocognitive dysfunction, and abnormal pulmonary function) (Ben Abraham et al. 2002; Dahlem et al. 2004a; Golder et al. 1998; Plotz et al. 2001; Weiss et al. 1996). The positive effects of lung-protective ventilation strategies have not yet been examined but should be regarded in clinical follow-up studies (Needham et al. 2005a, b). We need more structural follow-up of the children whose lives we saved (Knoester et al. 2007).

Barriers to implementing knowledge from bench to bedside still exist in critical care. Not every PICU worldwide is affiliated to an academic teaching center or medical school. Underestimation of ALI is reality. Physicians are reluctant to diagnose ALI except in its most extreme forms of ARDS. We need more awareness and feedback from the bench to the bedside and structural education (Rubenfeld et al. 2004; Wolthuis et al. 2007; Young et al. 2004). Due to the many anatomical and pathophysiological differences between adults and children, more research on the growing lung in children is warranted (Kornecki et al. 2005). Chest radiographs in children are mainly performed exclusively on

clinical judgement. Routine daily radiological assessment for ALI is uncommon. Left ventricular failure is an exclusion criterion by the AECC which, however, is not examined by pulmonary artery catheter in children and is diagnosed on clinical criteria or by echocardiography. Furthermore, left ventricular failure is not as common as in adult patients and has different underlying diseases in children. Therefore, a pediatric consensus conference defining ALI criteria for daily routine use and for scientific purposes is warranted. We have to find the special needs of our pediatric patients with respect to acute management, care, and follow-up. Comparisons with the results of adult studies should be minimized in the future.

Essentials to Remember

- Children have smaller airways with higher airway resistance, lower functional residual capacity (FRC), and more rigid chest wall than adults. These characteristics in anatomy and lung mechanics put children with ALI at higher risk of severe hypoxic respiratory failure.
- Clinical and experimental studies suggest that in patients with severe ARDS, lung-protective ventilation is established by sufficient positive end-expiratory pressure (PEEP), plateau pressure below 30 cm H₂O, and tidal volume (Vt) below 6 mL/kg.
- A pediatric ALI study (investigating the effects of prone position) observed in the control group with an average Vt not higher than 7 mL/kg and an average PEEP between 7 and 10 cmH₂O, the lowest mortality rate (only 8 %) yet ever reported (Curley et al. 2005).
- Appropriate ventilator settings search to restore or preserve FRC, if any possible.
- MV is only a supportive measure. Therapies should address the pathophysiological alterations in ALI.
- Studies about ALI/ARDS should differentiate between adult and pediatric patients.

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Educational Aims

In this chapter, we will:

- Consider the problem of bronchiolitis, its pathophysiology, and critical care therapy.
- Restrict discussion to clinical research evidence of RSV-induced lower respiratory tract disease wherever possible.
- Provide rational approaches to bedside mechanical ventilation.
- Focus on potential therapies that target the lower airway problem in respiratory system resistance and compliance.

November in the northern hemisphere, then your first winter exposure to RSV is likely to be when you are less than 4 months of age and vulnerable because of poor respiratory mechanical reserve (Alonso et al. 2007). However, if you are born in May/June, then you will be 7–8 months during your first winter exposure to RSV, much bigger and stronger and have more efficient thoracic and diaphragmatic mechanics. In the PICU, the main predictors of severe outcome in previously well infants appear to be young age, presence of apnea, and pulmonary consolidation on admission chest radiograph (Tasker et al. 2000; Lopez Guinea et al. 2007). Taken together, we can say that more severe RSV bronchiolitis in PICU practice is typically a problem of pulmonary consolidation, poor respiratory mechanics, and poor reserve, in the younger infant.

50.1 Introduction

Everyone on the planet is exposed to respiratory syncytial virus (RSV) infection by the age of 2 years. Most infants admitted to the pediatric intensive care unit (PICU) for respiratory support during this infection are previously healthy, but their principal risk for needing PICU treatment is young age. That is, if you are born in October/

50.2 Typical Features of Bronchiolitis and General Supportive Measures

The typical features of bronchiolitis in an infant less than 2 years of age are acute generalized peripheral airway obstruction, tachypnea, decreased breath sounds on auscultation, and low hemidiaphragms on chest radiograph. RSV is the most frequent cause of bronchiolitis. Other viral causes include adenovirus, influenza and parainfluenza, metapneumovirus, and rhinovirus. Cytomegalovirus can produce a bronchiolitis or pneumonitis-like illness in immunocompromised

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Table 50.1 Assessment and supportive therapies for RSV bronchiolitis

<i>Pulse oximetry should be performed in every child who attends hospital with acute bronchiolitis</i>
Infants with pulse oximetry oxygen saturation (SpO_2) $\leq 92\%$ require inpatient care
Decision about infants with SpO_2 between 92 and 94 % should be supported by detailed clinical assessment
Infants with $\text{SpO}_2 > 94\%$ in room air may be considered for discharge
<i>Supportive therapies for those admitted to hospital</i>
Nasal suction should be used to clear secretions in those with distress due to nasal blockage
Nasogastric feeding should be considered in infants who cannot maintain oral intake or hydration
Infants with $\text{SpO}_2 \leq 92\%$ or who have severe respiratory distress or cyanosis should receive supplemental oxygen by nasal cannulae or face mask
Infants may be considered for discharge when they can maintain $\text{SpO}_2 > 94\%$ in room air and more than 75 % of their usual daily oral intake
<i>Indication for acute assessment and high-dependency or intensive care referral</i>
Failure to maintain $\text{SpO}_2 > 92\%$ with increasing oxygen therapy or cyanosis
Recurrent apnea
Poor feeding ($< 50\%$ in the preceding 24 h) or lethargy
Presence of nasal flaring and/or grunting
Severe chest wall recession
Increasing respiratory distress and/or exhaustion despite supplemental oxygen. Blood gas analysis may have a role in the assessment of infants with severe respiratory distress

Based on SIGN (2006) guidelines

children. Rare, nonviral causes of bronchiolitis syndrome include *Mycoplasma pneumoniae* and *Bordetella pertussis* infection. The pathology of RSV infection in the lower airways is characterized by sloughed necrotic epithelium, excessive mucus secretion, bronchial mucosal edema, and peribronchial inflammation.

In this chapter, we will restrict the discussion and clinical research evidence to bronchiolitis and RSV-induced lower respiratory tract disease whenever possible. The focus will be on respiratory failure and PICU management, but the reader should be aware that most affected infants respond satisfactorily to oxygen therapy and general supportive measures. As an overview of this general therapy, Table 50.1 summarizes current guidelines and best evidence concerning assessment and hospital supportive measures for bronchiolitis in children (SIGN 2006).

tion are previously healthy and 10–40 % are less than 36 weeks’ gestational age (Law et al. 1997; Carbonell-Estrany et al. 2004). In individual series, prematurity and bronchopulmonary dysplasia have significant impact, and such cases are likely to require either high-dependency or intensive care (Greenough et al. 2001). The prediction of who will require PICU admission is not an exact science. Brooks et al. (1999) found in a population of 542 previously healthy term infants, where 1.8 % required admission, that tachypnea (respiratory rate $> 80/\text{min}$) and pulse oximetry arterial desaturation ($\text{SpO}_2 < 85\%$) had good specificity ($> 97\%$) but poor sensitivity ($\leq 30\%$) for predicting admission. The decision to admit to the PICU should depend on local referral practice and the ability to manage the problems outlined in Table 50.1.

50.3 Respiratory Failure in Bronchiolitis

A small proportion of cases of RSV bronchiolitis develop difficulties that are best managed in the PICU. Studies in the intensive care population suggest that 4–15 % of infants with RSV infec-

50.3.1 Patterns of Disease Requiring Mechanical Ventilation

There are no absolute indications for controlled mechanical ventilation (MV). The clinical situation should dictate what is required. For example, if a patient is being transferred between hospitals, patient safety during transfer may be the overriding

guiding factor. Alternatively, if a patient is being managed in a ward area within easy access of PICU practitioners, then it may be appropriate to wait until the infant demonstrates significant respiratory deterioration, such as those suggested by Rakshi and Couriel (1994):

- Persistent apneas with severe hypoxemia and $\text{pH} < 7.20$
- Altered mental state and $\text{SpO}_2 < 85\%$ with fractional inspired oxygen (FiO_2) above 0.6

The mechanism leading to progressive respiratory failure and apparent exhaustion will be discussed in later sections of the chapter (see Sects. 50.3.2 and 50.3.3). The other patterns of disease requiring MV are peripheral circulatory collapse, recurrent apneic attacks, and generalized convulsions (Simpson et al. 1974; Eisenhut 2006). Recurrent apnea in an infant, in the winter, should lead to the early diagnosis of bronchiolitis at the time of presentation. However, the diagnosis of underlying RSV infection may be overlooked in cases presenting with shock or hyponatremia-related seizures.

Apnea is common in RSV infection, particularly in those with a history of apnea of prematurity; it is usually nonobstructive (Anas et al. 1982). The mechanism of RSV-associated apnea is unclear, but possible explanations include stimulation of laryngeal chemoreceptors, sensitization of airway receptors, respiratory muscle fatigue, and abnormal immunologic responsiveness.

The shock-like state complicating RSV has been described by a number of authors (Simpson et al. 1974; Njoku and Kliegman 1993; Kim and Frankel 1997; Arnold et al. 2000; Checchia et al. 2000). There are some infants where the respiratory features of RSV infection are silent at presentation but can become severe enough to require high-frequency oscillatory ventilation (HFOV) (Arnold et al. 2000). There are others, where cardiac compromise is a consequence of cardiopulmonary interaction that improves with clinical improvement. For example, Sreeram et al. (1991) studied 21 infants with acute bronchiolitis, with normal hearts, and found that half had tricuspid valve regurgitation; many had evidence of raised pulmonary artery systolic pressure. In all such patients, myocardial injury may

contribute to the severity of presentation (Checchia et al. 2000).

Seizures during RSV infection usually result from hyponatremia (Simpson et al. 1974; Hanna et al. 2003), which is a consequence of the derangement in water, electrolyte, and endocrine homeostasis induced by high intrathoracic pressure (Gozal et al. 1990; Poddar et al. 1995). Typically, seizures cease once serum sodium is above 130 mmol/L.

50.3.2 Blood Gases and Respiratory Failure

Respiratory failure is not always present on admission to hospital, and progressive deterioration over a variable time period occurs in many such cases, which confirms the importance of clinical vigilance even in mild to moderately severe cases. Both components of respiration – carbon dioxide (CO_2) clearance and oxygenation – need to be assessed in infants with RSV infection.

In regard to CO_2 derangements in bronchiolitis, respiratory failure is defined as an arterial partial pressure of CO_2 ($P_a\text{CO}_2$) exceeding 65 mmHg (8.7 kPa). Reynolds (1963a) found that when such infants breathed air, there was little increase in $P_a\text{CO}_2$ above 40 mmHg, even when respiratory rates were up to 60 breaths/min (Fig. 50.1). At a breathing rate of 60 breaths/min, the arterial partial pressure of oxygen ($P_a\text{O}_2$) was ~60 mmHg (8 kPa). Downes et al. (1968) found two phases or a progression in CO_2 clearance. In infants with $P_a\text{CO}_2$ below 65 mmHg, the dead space-to-tidal volume ratio (V_D/V_T) was between 0.55 and 0.69. (In normal, spontaneously breathing infants, the ratio is 0.25 ± 0.07 , which is similar to that found in adults.) When increase in V_D/V_T originates within the respiratory system, it represents increase in V_D , decrease in V_T , or some combination of the two. Krieger and Whitten (1964) found lower mean V_T and mean minute volume in 24 infants with acute bronchiolitis; they concluded, “respirations may be considered shallow.” Distinct from these causes, outside of the respiratory system, hypovolemia or shock may also lead to high V_D/V_T . Given this limit to lung physiology in bronchiolitis, avoidance of

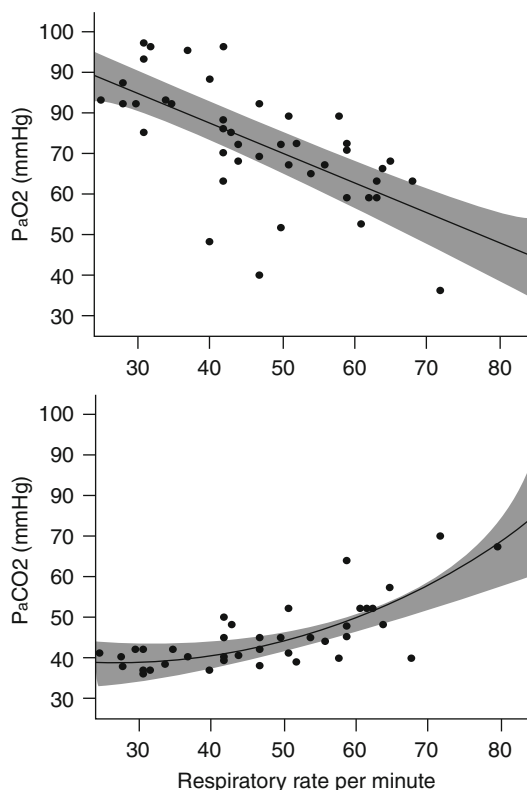


Fig. 50.1 Partial pressure of oxygen (P_aO_2) and carbon dioxide (P_aCO_2) plotted against respiratory rate in infants with bronchiolitis who are spontaneously breathing room air (Figures redrawn from Reynolds (1963a) with additional regression analysis and 95 % confidence interval for fitted lines)

respiratory failure can be accomplished by maintenance of two- to threefold increase in minute volume (Downes et al. 1968). In bronchiolitis, if V_T is limited, then compensatory increase in minute ventilation has to be due to an increase in respiratory frequency (Stokes et al. 1981). It is interesting to note that infants with respiratory failure (based on clinical and blood gas findings) have high V_D/V_T associated with minute ventilation close to predicted basal levels, which implies that the needed increase in minute ventilation has not been maintained. At this point, some infants are extremely tachypneic, so their deterioration represents worsening increase in V_D or lessening of V_T . In other infants, this state represents fatigue or an abnormality in lung mechanics that cannot be overcome. Of note, the V_D/V_T remains raised

(0.46 ± 0.10) even after starting MV, which is due to increase in physiologic dead space caused by hyperinflation or associated hypoperfusion (Almeida-Junior et al. 2007).

Clinical assessment of oxygenation – particularly hypoxia – is difficult in bronchiolitis (Simpson and Flenley 1967). Cyanosis is invariably present when SpO_2 is below 85 %, but this is a late sign. There is a significant inverse relationship between respiratory rate and P_aO_2 (Reynolds 1963a). In those breathing air, respiratory rate increases from 25 to 60 breaths/min as P_aO_2 falls from 90 to 60 mmHg (Fig. 50.1). There is also a significant inverse linear correlation between P_aCO_2 and P_aO_2 , which suggests that alveolar hypoventilation contributes to arterial hypoxemia (Downes et al. 1968). From first principles, in the Downes et al. data, the degree of hypoxemia is as expected from the alveolar gas equation and a normal alveolar-arterial oxygen ($AaDO_2$) gradient: at a time when P_aCO_2 is 65 mmHg (and assuming a respiratory quotient of 0.8), the expected alveolar PO_2 is 68 mmHg, which is consistent with the P_aO_2 of 50 mmHg observed. However, Reynolds (1963b) found much higher $AaDO_2$ in 10 infants with bronchiolitis, ranging from 35 to 57 mmHg, and concluded that since administering oxygen (fractional inspired oxygen, FiO_2 , 0.4) made their P_aO_2 rise to above 100 mmHg (13.3 kPa), the most likely cause of large $AaDO_2$ gradient was ventilation-perfusion inequalities. As the condition becomes extremely severe, intrapulmonary shunt may become the more significant cause of high $AaDO_2$ (Tasker et al. 2000).

Taken together, it is likely that abnormal gas exchange in bronchiolitis is produced by rise in V_D/V_T and worsening ventilation-perfusion inequalities. In less severe states, the former is compensated by increase in minute ventilation. In more severe disease, there is failure in this compensation. The critical questions are as follows: what is driving tachypnea, and what is causing V_D/V_T to increase? Rising P_aCO_2 is not the stimulus for rapid breathing, since respiratory rate is increased despite near-normal levels. Neither is P_aO_2 the stimulus, since this parameter increases respiratory rate when <60 mmHg.

50.3.3 Lung Function and Mechanics in Bronchiolitis

The total work that has to be performed on the lung proper is the work necessary to overcome both elastic and nonelastic resistance. In addition to elastic and nonelastic resistance, respiratory work is a function of rate and V_T . Work of breathing in bronchiolitis is double to six times that of normal infants but similar to that of infants with bronchopneumonia (Krieger and Whitten 1964; Stokes et al. 1981). Interestingly, the latter do not present in extremis, which implies that this increase in work of breathing can be tolerated, but the problem may lie in whether lung mechanics in bronchiolitis permit such work. Since individual clinical features (e.g., auscultation, respiratory rate, and heart rate) do not correlate with total work of breathing, it is difficult to assess (Stokes et al. 1981). The degree of hyperinflation may be helpful in the assessment because it does mirror severity, but the best measure of work is esophageal pressure changes during breathing.

Given the obstructive lesions in terminal bronchioles in bronchiolitis, we would expect high nonelastic resistance. Yet, in general, infants with bronchiolitis do not show prolongation of the expiratory phase. They also breathe rapidly, which is inefficient when there is increased resistance to airflow. In one series of acute bronchiolitis, mean nonelastic resistance was similar to that of normal infants of similar age distribution (~ 0.03 cm H₂O/mL/s) (Krieger 1964). This finding can be explained by the theory of “equality of time constants,” i.e., when flow is rapid in a system of unequally obstructed airways, the measured resistance will approximate that of the large peripheral pathways (Otis et al. 1950).

In contrast to the normal findings in nonelastic resistance, elastic resistance is high in bronchiolitis, which also means that compliance is markedly decreased (Krieger and Whitten 1964; Panitch et al. 1993; Smith et al. 1993). This decrease in compliance is due, in part, to rapid respiratory rates (Helliesen 1958) and bronchiolar inflammation. The most significant factor, however, is the increased retractive force that is

active at a high level of lung inflation; the degree of lung distention (i.e., V_T) influences work expenditure more significantly when compliance is low. (Speed of distention, i.e., respiratory rate, is a more important influence when airflow resistance is increased.) Krieger and Whitten (1964) found that elastic work was less than expected in bronchiolitis. The rapid shallow mode of breathing, therefore, appears to be economical in terms of work expenditure when compliance is low (Otis et al. 1950), because elastic work is conserved through breathing fast. These points are illustrated in the two cases of bronchiolitis depicted in Fig. 50.2. The relationship between elastic ($1/\text{compliance}$), viscous (resistance), and total work of breathing per minute to frequency of breathing during bronchiolitis and on recovery is shown in graphs that have been calculated from first principles according to the equations described by Otis et al. (1950). The acute and convalescent data are from two cases of bronchiolitis reported by Krieger and Whitten (1964). The upper two panels (A and B) are from a 5.5 kg infant with, predominantly, reduced compliance. The lower two panels (C and D) are from a 4.5 kg infant with a mixed abnormality in compliance and resistance. The acute graphs (A and C) show a doubling of total work, due mainly to increased elastic work. The vertical lines show the infant’s respiratory rate and where this rate intersects the work curves.

“Exhaustion” in infants with bronchiolitis does not result from extreme work during breathing. It is more likely a phenomenon of inability to perform the workload necessary for breathing using hyperinflated lungs. In bronchiolitis, hyperinflation places the muscles of inspiration at a mechanical disadvantage; they are unable to shorten sufficiently to produce the necessary reduction in intrapleural pressure. Another physiologic problem that is considered to follow from obstructive breathing with large negative intrathoracic pressure swings (unbalanced by similar positive pressure efforts) is transpulmonary fluid shifts and the development of pulmonary edema (Stalcup and Mellins 1977). Stokes et al. (1981) did not find evidence for this phenomenon in 26 hyperinflated infants with bronchiolitis. Instead,

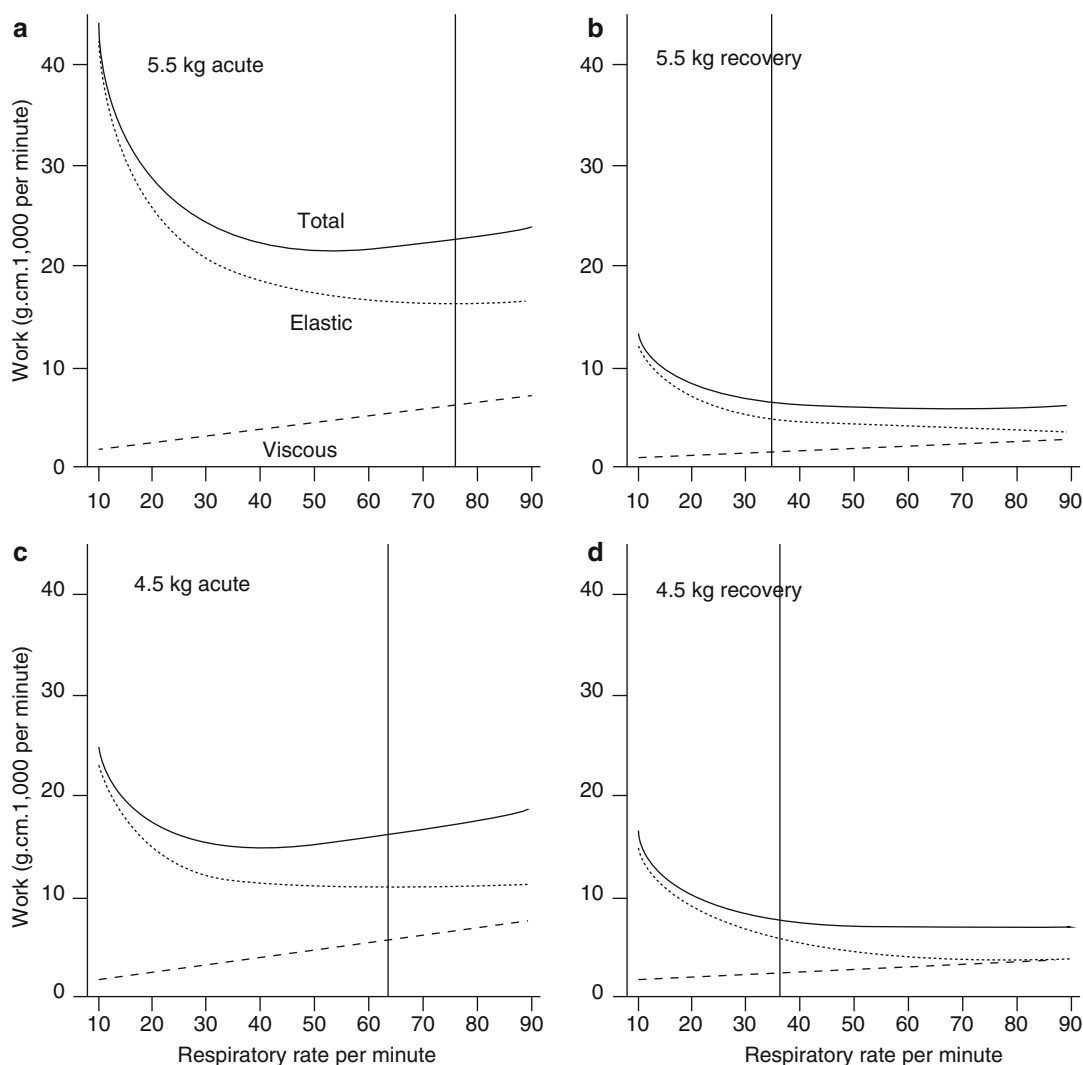


Fig. 50.2 Relationship of elastic, viscous, and total work of breathing per minute to frequency of breathing, during the acute and recovery phase of bronchiolitis. Graphs **a** and **b** refer to a 5.5 kg infant; graphs **c** and **d** refer to a 4.5 kg infant. The data are calculated according to the equations derived by Otis et al. (1950) using real data from two infants reported by Krieger and Whitten (1964) and assuming V_D/V_T changes from acute to recovery, of 0.45–0.25 (see Almeida-Junior et al. 2007). In the acute

graphs (**a** and **c**), total work of breathing is increased compared with the recovery phase. Elastic work decreases with increasing respiratory rate, and viscous work increases with increasing respiratory rate. It is more efficient to breathe at higher respiratory rate during bronchiolitis as demonstrated by the vertical lines that show the breathing rate of the infant during each stage of illness. The recovery graphs (**b** and **c**) show optimum respiratory rate as lung mechanics improve

the esophageal pressure monitoring in these infants showed positive values for a large portion of the respiratory cycle, which suggests that positive pressures were produced on expiration. Fluid flux across the alveolar-capillary membrane would be avoided in this state because of limited hydrostatic pressure gradient.

50.4 Respiratory Support for Bronchiolitis

The lung abnormalities in RSV bronchiolitis are hyperinflation, impaired minute ventilation, impaired ventilation-perfusion matching, and an increase in physiologic dead space. As a

consequence, the infant breathes rapidly and has increased elastic and viscous work of breathing. By the time that respiratory support is considered, hypercarbia and hypoxemia are also present. In this setting, *the aim of respiratory support is to overcome the exaggerated work of breathing and abnormal lung mechanics and allow for resolution of the primary pathophysiology.*

Most infants with respiratory failure have “obstructive” lung mechanics, but abnormality in compliance often coexists (Fig. 50.2). The discussion in previous sections (see Sects. 50.3.2 and 50.3.3) indicates that infants with progressive deterioration exhibit a continuum with lessening reserve and compromised homeostasis. A reasonable question, then, is to ask whether this progression can be limited. For example, it is the interaction between the patient’s drive to breathing and abnormal lung mechanics that leads to deterioration and ultimately respiratory failure. So why not intervene early to limit the effect of interaction between drive to breathing and lung mechanics? Altering lung mechanics or altering the effect of interaction between spontaneous breathing and lung mechanics could achieve this result.

50.4.1 Noninvasive Respiratory Support

Sixteen percent of infants hospitalized for RSV have apnea, and its course is usually short-lived. Clinically, these episodes are diaphragmatic or nonobstructive with complete absence of respiratory effort. In these cases, most clinicians would consider that endotracheal intubation with minimal ventilatory support is required until the problem resolves. However, McNamara and Sullivan (1997) reported an improvement in RSV-infection-related apnea with the use of nasopharyngeal prong continuous positive airway pressure (CPAP) alone.

We now know that patients with worsening respiratory distress due to hyperinflation can be supported without using endotracheal intubation. To date, three ways of delivering CPAP have been applied and reported:

- Heated, humidified, high-flow nasal cannulae (HFNC)
- Nasopharyngeal CPAP
- Nasopharyngeal bilevel positive airway pressure (BIPAP)

CPAP maintains positive transpulmonary pressure during spontaneous breathing. It keeps the airways open by moving the equal pressure point more proximal in the airways, such that airway collapse does not occur. It increases secretion clearance. It improves compliance and reduces the work of breathing. Last, it improves gas exchange. However, the cost of these benefits is that its use may lead to lung overinflation.

50.4.2 Heated Humidified High-Flow Nasal Cannulae

HFNC is a relatively new therapy that allows the delivery of high inspired gas flows (1–8 L/min in infants) with or without increased oxygen concentration (McKiernan et al. 2010). Ideally, these devices should deliver flow greater than the patient’s peak inspiratory demand to fully support their minute ventilation. In addition, HFNC provides some level of CPAP, which depends on the flow delivered relative to the size of the patient and on the leak around the nasal cannulae. Flows of 3–5 L/min in term infants have been shown to generate intrapharyngeal pressure of up to 5 cm H₂O (Spence et al. 2007). The advantages of this system over conventional nasal CPAP delivery devices are that it is less cumbersome, better tolerated, and as a consequence used earlier. The disadvantage of this system is that not all attendants may realize that HFNC is CPAP by another name – it isn’t just nasal oxygen. As a consequence, clinical deterioration while receiving HFNC means failed low-level CPAP. McKiernan et al. (2010) reported their PICU experience of managing infants with RSV bronchiolitis before and after the introduction of HFNC to their practice. In the season after the introduction of HFNC, only 9 % of infants required intubation, compared with 23 % in the previous season ($P=0.04$). HFNC decreased respiratory rate to a greater extent than other

devices, and those with the greatest decrease in respiratory rate were least likely to be intubated. The authors also found that median PICU length of stay for cases of bronchiolitis decreased from 6 to 4 days.

50.4.3 Nasal CPAP

We know that in very preterm neonates, early nasal CPAP at birth reduces the number of days of MV (Morley et al. 2008). We also know that application of CPAP to nasal mask better reduces work of breathing when compared with the effect of CPAP applied to an endotracheal tube (Keidan et al. 2000; Pandit et al. 2001). This difference is most likely due to improved patency of the upper airway, rather than major increases in functional residual capacity (FRC) and lung compliance. In view of this theory, we should expect that early intervention with CPAP in bronchiolitis should reduce the work of breathing and may even obviate the need for endotracheal intubation and more invasive support.

Beasley and Jones (1981) reported the use of nasal CPAP early in the course of acute bronchiolitis in 14 infants. They found it improved gas exchange and was free of complications. Thia et al. (2008) showed, in a randomized controlled trial, that there is indeed a reduction in $P_a\text{CO}_2$ when using CPAP. This reduction was better if CPAP was used first than if it was used after a 13-h period with standard treatment. The success rate of noninvasive support in bronchiolitis found in other studies varies from 75 to 83 % (Soong et al. 1993; Campion et al. 2006; Larrar et al. 2006).

50.4.4 BIPAP

Javouhey et al. (2008) reported an approach that bridges the step-up in support between noninvasive airway pressure support and assisted ventilation. These investigators used noninvasive ventilation as their primary form of respiratory support in 27 infants with bronchiolitis. Their initial care was CPAP at 5–10 cm H₂O. If this support failed, they progressed to BIPAP starting

at 12 cm H₂O and, thereafter, gradually increasing to 18 cm H₂O with a backup rate at 30 breaths/min. Compared with their previous experience of similar severity infants, this PICU found that the rate of endotracheal intubation was significantly lower (89 % vs 52 %, $P < 0.01$) and, not surprisingly, the rate of ventilator-associated pneumonia was also much reduced.

50.5 Invasive Conventional Mechanical Ventilation

Mechanical ventilation in RSV bronchiolitis has as its goal patient stability; restoring adequate gas exchange and unloading the work of respiratory muscles bring about this state. The problem is that we are constrained by abnormal lung mechanics and the natural history of the condition. The current practice of respiratory support for bronchiolitis is largely based on clinical judgement and local experience, rather than any consensus (Leclerc et al. 2001). Yet despite this source for variation, the time course of admission on the PICU is remarkably consistent. Cases with no preceding or underlying disease intubated for apnea or respiratory deterioration will require MV for 4–5 days, on average. Cases with preceding disease are ventilated much longer, on average for up to 3 weeks (Stretton et al. 1992; Tasker et al. 2000).

50.5.1 Initial Settings for Mechanical Ventilation

A review of MV settings applied to infants with RSV – reported in the literature 1967–1994 – reveals considerable variation in practice (Table 50.2). Both volume-cycled and pressure-cycled MV are described in the literature with breathing rates varying from 10 to 60 breaths/min, maximum pressures from 20 to 50 cm H₂O, and V_T from 6 to 20 mL/kg (Leclerc et al. 2001). There is no evidence for a superior mode of MV, and it would be difficult to plan such a study since mortality and morbidity are low and, as noted above, time course on PICU is fairly consistent. We are therefore left with a pragmatic

approach that takes account of the prevailing pathophysiology. Figures 50.3 and 50.4 illustrate this point. The inflation-deflation volume curves above FRC are hypothetical for a model 5 kg

Table 50.2 Ventilator settings used in infants with RSV (1967–1994)

Variable	Value
Ventilator rate (breaths/minute)	10–15 to 30–60
Maximum peak inspiratory pressure (cm H ₂ O)	20–25 to 30–50
Positive end-expiratory pressure (cm H ₂ O)	3–15
Tidal volume (mL/kg)	6–20

Based on data reviewed by Leclerc et al. (2001)

infant and based on data presented in the literature. (The curves are a simplification of the ideal situation with a number of assumptions – see figure legend – but they do illustrate the physiology). The “control” cases in Fig. 50.3 represent the mean data for controls in the report by Hammer et al. (1997): if one chose to ventilate a 5 kg infant at a rate of 30 breaths/min with inflation pressure (P_{inf}) of 16 cm H₂O, we may expect $P_a\text{CO}_2$ 35 mmHg. The “bronchiolitis” cases in Fig. 50.3 represent the mean data for the unselected cases of bronchiolitis reported by Derish et al. (1998). If we make the assumption that there is an increase in V_D/V_T ratio during

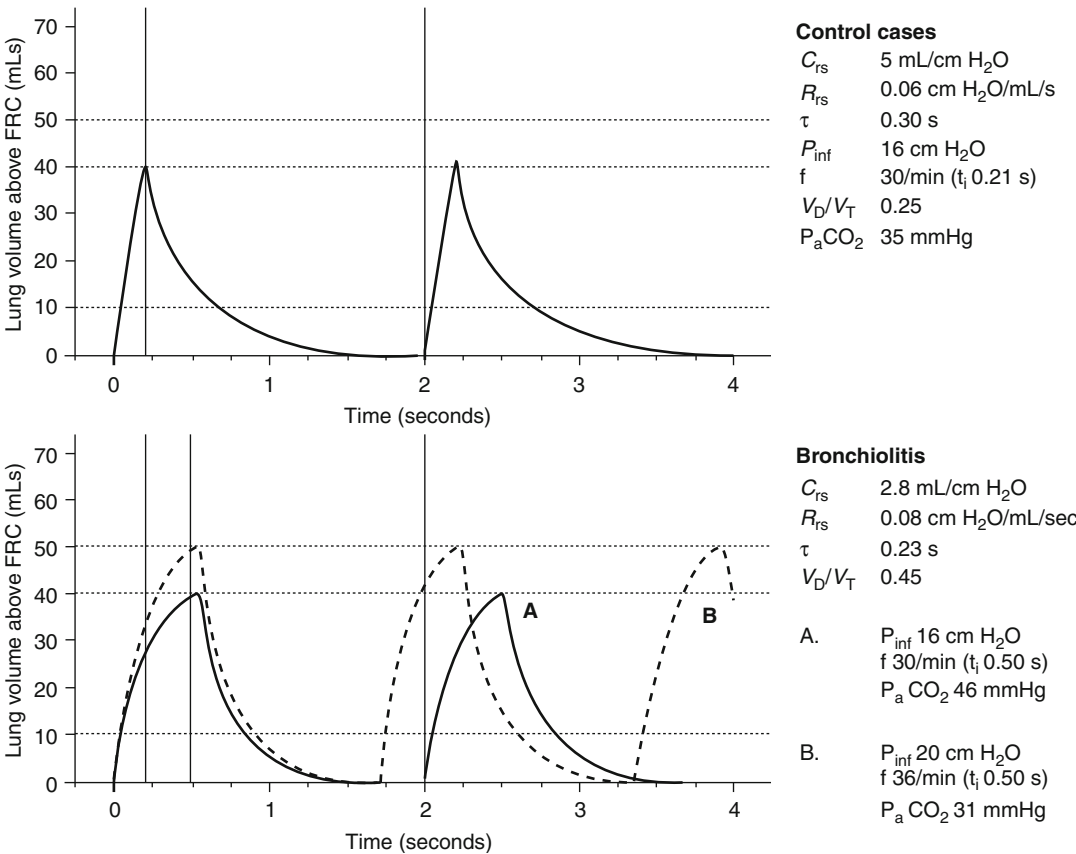


Fig. 50.3 Calculated time course of inflation and deflation curves for artificial ventilation by intermittent application of constant pressure (*square wave*) followed by passive expiration. The graphs are normalized for a model 5 kg infant and assume full sedation and neuromuscular blockade, where C_{rs} is respiratory system compliance, R_{rs} is respiratory system resistance, τ is the time constant, P_{inf} is the inflating pressure, f is the ventilation frequency, t_i is the inspiratory time, and V_D/V_T is the

space-to-tidal volume ratio. The “control” cases are the 26 controls in the series reported by Hammer et al. (1997). The “bronchiolitis” cases are the 25 cases reported by Derish et al. (1998). $P_a\text{CO}_2$ is estimated from the available data and assumes weight of 5 kg and constant respiratory quotient (0.86) and CO_2 production across groups. See text for details. The definitions of curves **A** and **B** are shown in the column

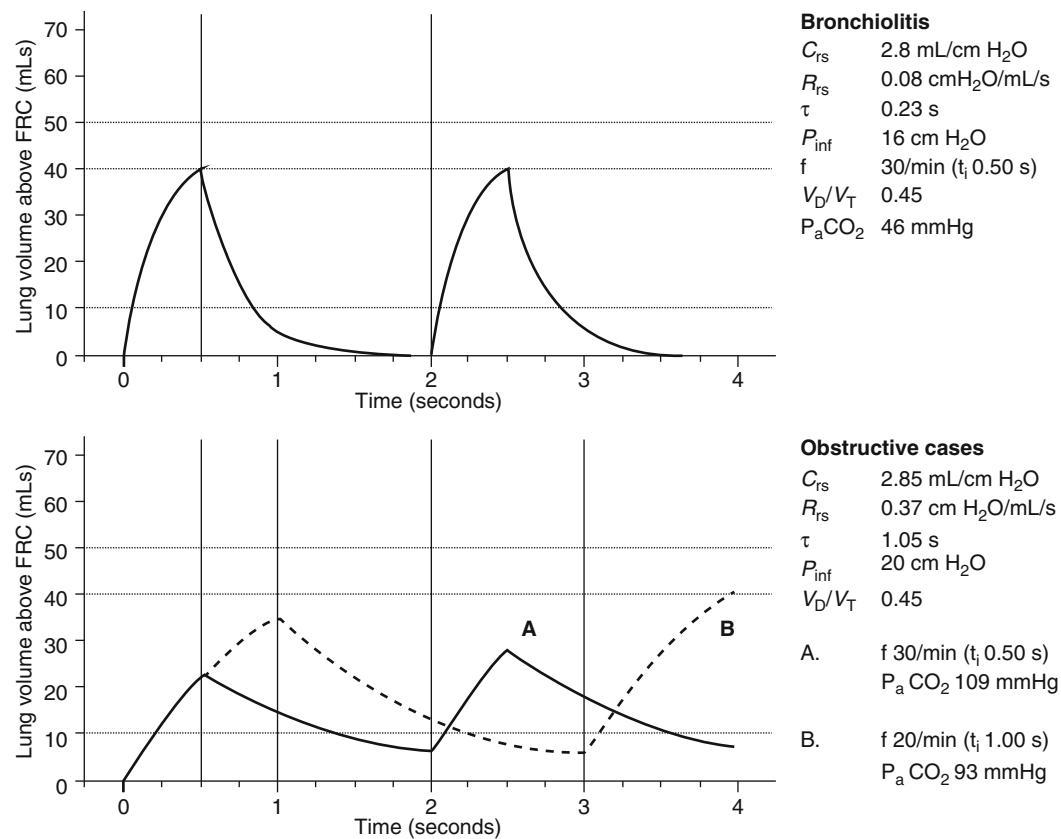


Fig. 50.4 Calculated inflation and deflation curves for “bronchiolitis” and “obstructive” cases. The nomenclature and assumptions are the same as Fig. 50.3. The “bronchiolitis” cases are the 25 cases reported by Derish et al. (1998). The

“obstructive” cases are the 27 selected cases reported by Hammer et al. (1997). See text for details. The definitions of curves A and B are shown in the column

bronchiolitis (Almeida-Junior et al. 2007) as well as a change in respiratory system compliance (C_{rs}) and resistance (R_{rs}), continuing to ventilate a 5 kg infant at a rate of 30 breaths/min with P_{inf} 16 cm H₂O will result in P_aCO_2 46 mmHg (graph A). Note that the inspiratory time (t_i) has been increased to 0.50 s to allow inflation lung volume above FRC to reach 40 mL (i.e., 8 mL/kg). If the t_i had remained the same as in “controls,” inflation lung volume above FRC would only be 3 mL/kg. Graph B shows the potential danger of responding to P_aCO_2 46 mmHg with simultaneous increases in P_{inf} to 20 cm H₂O and ventilator frequency to 36 breaths/min. Lung volume above FRC rises to 10 mL/kg, and P_aCO_2 falls to hypocapnic level (i.e., 31 mmHg).

Figure 50.4 shows the “bronchiolitis” data from Derish et al. (1998). The upper panel is the

same as graph A in Fig. 50.3 and is used for comparison. The “obstructive” cases represent the mean data for the cases selected as “obstructive” bronchiolitis reported by Hammer et al. (1997). These cases had more severe disease than those reported by Derish et al. (1998). The main difference is that the cases reported by Derish et al. (1998) have an isolated fall in C_{rs} , whereas the cases reported by Hammer et al. (1997) have a fall in C_{rs} and increase in R_{rs} . Graph A shows the inadequacy of ventilation at a rate of 30 breaths/min and a t_i (0.50 s) similar to that for the “bronchiolitis” cases, even though the P_{inf} is increased to 20 cm H₂O. The estimate of P_aCO_2 is now 109 mmHg. The deflation curve also shows the development of dynamic hyperinflation (see end-expiratory volume above zero). Graph B shows the effect of lengthening t_i and decreasing the

ventilator rate. The problem of dynamic hyperinflation continues, but tidal volume is improved. $P_a\text{CO}_2$ is nowhere near being fully controlled (i.e., 93 mmHg), but further increase of P_{inf} , lengthened t_i , and slower ventilator frequency will bring $P_a\text{CO}_2$ to more tolerable levels.

These examples highlight the clinical reality of ventilatory management of bronchiolitis. In less severe cases, with modest decrease in C_{rs} , standard approaches should not cause harm providing ventilator rates are limited to 30 breaths/min. In more severe cases, in the absence of lung function testing, clinical observation of inspiratory and expiratory chest excursion as well as regular auscultation is important. The aim in the “obstructive” lung is to avoid overventilation, with associated hyperinflation, and barotrauma. Ventilatory management should therefore take account of two guiding principles:

- Achieve adequate but not necessarily normal arterial blood gases. Adequate oxygenation is considered present with $P_a\text{O}_2 > 60$ mmHg (8 kPa) or $\text{SpO}_2 > 88\%$. Adequate minute ventilation is considered present with any value of $P_a\text{CO}_2$ that achieves $\text{pH} > 7.25$ (so-called permissive hypercapnia strategy; see Sect. 50.6.1).
- Avoidance of overdilation of hyperinflated lungs by limiting V_T to 6–8 mL/kg. This goal may even necessitate MV at slow ventilation rates (10–15 breaths/min) with prolonged expiratory times to limit ventilator-associated dynamic hyperinflation and impaired minute ventilation. (MV of “restrictive” lungs is discussed in Sect. 50.6). Our recommendation is that ventilator rate should be limited < 30 breaths/min.

All infants will require adequate analgesia and sedation during MV. Morphine (20–40 $\mu\text{g/kg/h}$), chloral hydrate (30–50 mg/kg every 4 h), and midazolam (50–250 $\mu\text{g/kg/h}$) are commonly used. In combination, these drugs will alter the CO_2 -ventilatory response, with a decrease in the slope and an increase in the apnea threshold (Yaster et al. 1990). These features are useful when applying the permissive hypercapnia strategy (see Sect. 50.6.1). However, these effects may be detrimental after extubation since the expected protective response to worsening gas

exchange will be blunted, hence the need for continued close observation 12–24 h after extubation (see 4.5.3). When neuromuscular blockade is required, vecuronium (50–100 $\mu\text{g/kg/h}$) can be used. The main reason for neuromuscular blockade is to enable MV at either very slow rates or fast (HFOV) rates and prevent ventilator-patient asynchrony. As will be discussed later, neuromuscular blockade is not necessarily required during HFOV (see Sect. 50.6.2).

50.5.2 Positive End-Expiratory Pressure

In all intubated patients, the removal of intrinsic positive end-expiratory pressure (PEEP) and lowering of end-expiratory volume necessitates the use of applied PEEP in order to avoid atelectasis. However, the use of PEEP in bronchiolitis is controversial. Not all centers use it, but in those that do, it is used at levels between 3 and 15 cm H_2O (Table 50.2). In bronchiolitis, low-level PEEP during MV is used with the idea that it decreases airway resistance and improves gas exchange (Wren et al. 1982; Frankel et al. 1986). But it is also possible that PEEP may not have these desired effects in bronchiolitis because airways of such infants are smaller and may not be distensible. To date, studies of lung mechanics and PEEP have shown varied results (Smith et al. 1993; Gauthier et al. 1998; Marchal et al. 1998). Smith et al. (1993) studied the effect of increasing PEEP in steps of 3 cm H_2O (0–9 cm H_2O) and found that applied PEEP at any level failed to consistently improve passive expiratory airway resistance or increase compliance from baseline. Inadvertent or auto-PEEP (i.e., the accompanying residual airway pressure at end expiration in MV patients) occurred in all cases (5 ± 2 cm H_2O), but it had no influence on the response of mechanics to applied PEEP, except that peak inspiratory pressures increased when applied PEEP was greater than auto-PEEP. (It should be noted that the presence of auto-PEEP requires that applied PEEP be set at the same level in order to optimize expiratory flow.) In contrast to the Smith et al. (1993) findings, Gauthier et al.

(1998) contend that there may be an optimum level of PEEP in acute bronchiolitis (Marchal et al. 1998).

When RSV lower respiratory tract disease is complicated by parenchymal restrictive disease – usually associated with some obstructive component – an adequate level of applied PEEP is certainly needed (Hammer et al. 1997) (see Sect. 50.6). Last, when significant levels of PEEP are being used, it should not be forgotten that it will further complicate the cardiac-pulmonary-renal interaction of bronchiolitis that results in abnormal water and electrolyte homeostasis (Gozal et al. 1990; Poddar et al. 1995). Therefore, whenever PEEP is used, fluids, electrolytes, and hydration must be closely monitored. Our practice is to restrict water to 67–75 % of maintenance requirements. Careful attention should also be given to cardiac function and the need for volume and inotropes (Simpson et al. 1974; Njoku and Kliegman 1993; Kim and Frankel 1997; Arnold et al. 2000; Checchia et al. 2000).

50.5.3 Airway Obstruction in Mechanically Ventilated RSV Bronchiolitis

A few studies have assessed pulmonary function and the use of bronchodilators to treat airway obstruction during MV for the very acute stage of RSV bronchiolitis (Mallory et al. 1989; Smith et al. 1990; Hammer et al. 1995, 1997). One limitation in assessing R_{rs} , and therefore making some conclusion about airway obstruction, is that the measurement is codependent on airway caliber and lung volume; bronchodilation and decrease in air trapping have opposite effects, and few studies have reported lung volume changes. Hammer et al. (1995, 1997) found that most infants requiring intubation and MV have evidence of obstructive airway disease with reduced flows, air trapping, and a component of restrictive lung disease. Albuterol inhalation affected either all or none of the measured lung functions; if a decrease in R_{rs} occurred, it was always accompanied by a reduc-

tion in air trapping. Figure 50.5 illustrates this point. The nomenclature is the same as Fig. 50.3. The figure uses the mean data of “obstructive” patients reported by Hammer et al. (1997). The upper panel shows that in these selected patients (more severe than the cases reported by Derish et al. (1998); see above), MV with a rate of 20 breaths/min (t_i 1.00 s) and P_{inf} 20 cm H₂O would result in P_aCO_2 93 mmHg. The middle and lower panels show the hypothetical effect of influencing either R_{rs} or C_{rs} or both together. Graph A in the middle panel shows the effect on inflation and deflation of halving R_{rs} from 0.38 to 0.19 cm H₂O/mL/s. Lung volume above FRC is increased, and there is reduction in dynamic hyperinflation. The theoretical consequence on P_aCO_2 is a reduction from 93 to 58 mmHg. Graph B in the middle panel shows the effect of increasing C_{rs} from 2.85 to 4.28 mL/cm H₂O. Dynamic hyperinflation is worsened, and there is no improvement in P_aCO_2 . Graphs A and B in the lower panel show the combined effect of making the above changes in R_{rs} and C_{rs} but simultaneously rather than separately. Graph A shows that dynamic hyperinflation remains, but there is the additional problem of overinflation with tidal volume 12 mL/kg. Initially, P_aCO_2 will be driven down even further to 49 mmHg. Graph B shows that decreasing t_i from 1.00 to 0.75 s will lessen the effect of dynamic hyperinflation (estimated P_aCO_2 62 mmHg), but an even slower ventilator rate may be needed.

Figures 50.3, 50.4, and 50.5 show heterogeneity in the physiology of bronchiolitis. It is therefore not surprising that the usefulness of β_2 -adrenergic drugs (e.g., salbutamol and albuterol) remains controversial in standard clinical practice. The results of studies are mixed, and many infants fail to show clinically significant improvement, but this finding is probably a reflection of the variation in (or lack of) abnormality in R_{rs} (Derish et al. 1998). There is also some evidence that combined β - and α -agonists (e.g., epinephrine) are more effective, because of their additional vasoconstrictor effects, which decrease bronchial mucosal edema and hence airflow obstruction (Sanchez et al. 1993; Menon et al. 1995; Numa et al. 2001). These

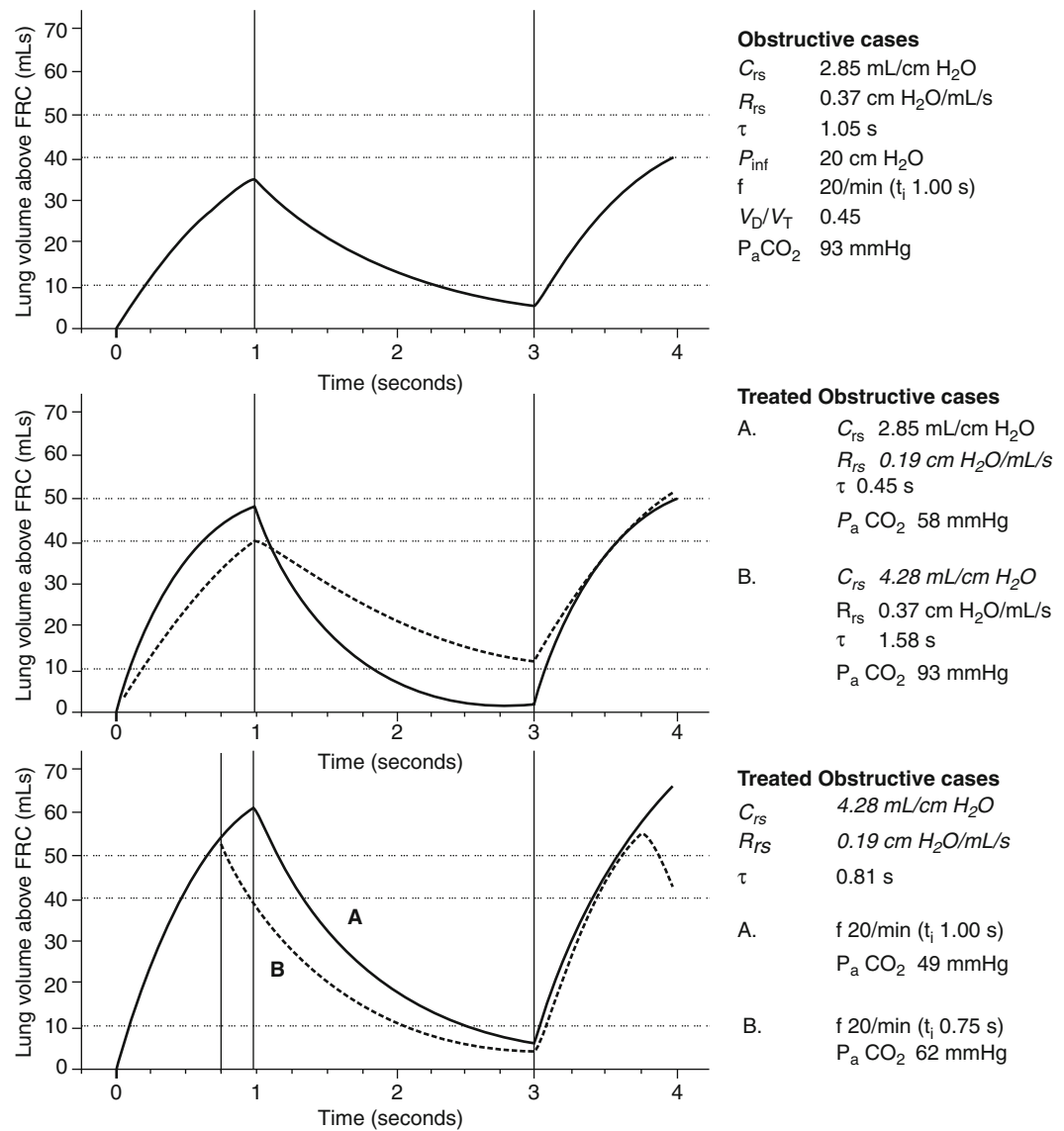


Fig. 50.5 Calculated inflation and deflation curves for “obstructive” bronchiolitis and the theoretical response to changes in lung function. The nomenclature and assumptions are the same as Fig. 50.3. The “obstructive” cases

are the 27 selected cases reported by Hammer et al. (1997). See text for details. The definitions of **A** and **B** curves are shown in the column

potential beneficial effects, however, may be outweighed or masked by other drug effects having an opposite influence on blood gases. For example, all of these drugs increase total body oxygen consumption, minute ventilation, and energy requirement by their direct or indirect effects on other organs through β -receptor stimulation (Newth et al. 1997b).

50.5.4 Weaning from Mechanical Ventilation

Weaning from MV is achieved by the gradual reduction of ventilatory support until spontaneous breathing can be fully resumed. No single variable or marker can predict progression of MV towards extubation. There are a variety of existing surrogate

markers that we use to reflect major components of the respiratory system including ventilatory drive, ventilatory reserve, and efficiency of gas exchange. These include respiratory frequency, V_T , minute ventilation, gas diffusion (P_aO_2 , P_aCO_2 , $AaDO_2$) and pH, muscle strength, SpO_2 , and heart rate.

In practice, patients are removed from ventilatory support when the attendant considers it is safe to do so from first principles. In regard to blood gas parameters, this means adequate oxygenation in a $FiO_2 < 0.4$ and normal pH with good respiratory drive in the absence of hypercarbia. Discharge from the PICU can be considered once the patient has managed at least 12–24 h without any respiratory assistance (see Sect. 50.5.1).

50.6 Acute Respiratory Distress Syndrome and RSV

On average, most MV patients with RSV bronchiolitis will spend less than 7 days on the PICU (Tasker et al. 2000). If there is a deviation from this trajectory, then it is important to consider whether the course of illness is complicated by another process such as infection. For example, up to 40 % of patients admitted with severe RSV bronchiolitis are infected with bacteria in their lower airways and are at increased risk of bacterial pneumonia. Thorburn et al. (2006) undertook a prospective microbiological analysis of lower airway secretions in all RSV-positive bronchiolitis, MV patients on admission to their PICU during three consecutive RSV seasons. Seventy of 165 children (42.4 %) had lower airway secretions positive for bacteria; 36 (21.8 %) were coinfectd. If higher ventilator rates are considered necessary (and tolerated), then the operator should consider whether the infant really does have bronchiolitis physiology. If mean airway pressure is above 10 cm H_2O and $AaDO_2$ above 400 mmHg, then the possibility of pulmonary restrictive disease should be considered (Hammer et al. 1997; Tasker et al. 2000). In this setting, the aim of MV is to recruit lung volume with the addition of PEEP and to limit barotrauma by limiting V_T to less than 8 mL/kg.

In RSV lower respiratory tract disease, two distinct patterns in lung function changes have been

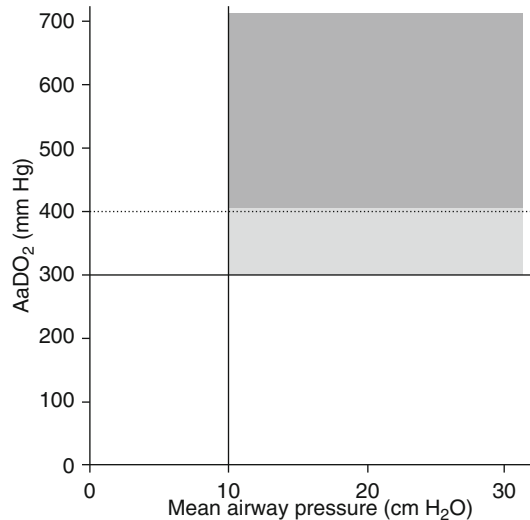


Fig. 50.6 Plot of best mean airway pressure and alveolar-arterial oxygen gradient ($AaDO_2$) from the first 48 h of mechanical ventilation. Patient data that falls within the darker shaded region within the first 24 h or lighter shaded region within the second 24 h reflects severe disease (i.e., likely acute respiratory distress syndrome or severe restrictive disease) with high sensitivity and specificity (Redrawn from Tasker et al. (2000))

identified (Hammer et al. 1997; Newth et al. 1997a). As noted above, most infants suffer from an “obstructive” pattern of disease (i.e., mixed change with modest fall in C_{rs} and increase in R_{rs}). Severe “restrictive” parenchymal disease (i.e., severe fall in C_{rs}), usually referred to as pneumonitis, is seen in those whose condition is often compatible with a diagnosis of acute respiratory distress syndrome (ARDS) (Patel et al. 1999; Tasker et al. 2000). ARDS is defined clinically using the criteria recommended by the American-European consensus (Bernard et al. 1994): acute disease onset, P_aO_2/FiO_2 ratio ≤ 200 mmHg, bilateral infiltrates on chest radiograph, and the absence of clinical evidence of left atrial hypertension. Patients with RSV-induced ARDS are, in general, younger and have a longer time course on MV. Tasker et al. (2000) reported that 20 % of MV infants have this pattern of disease and their usual time course is at least 2 weeks on the PICU. These infants demonstrate significant intrapulmonary shunt with best $AaDO_2 > 400$ mmHg within the first 48 h of MV (Fig. 50.6). The strategies that are used in RSV-related ARDS are discussed below.

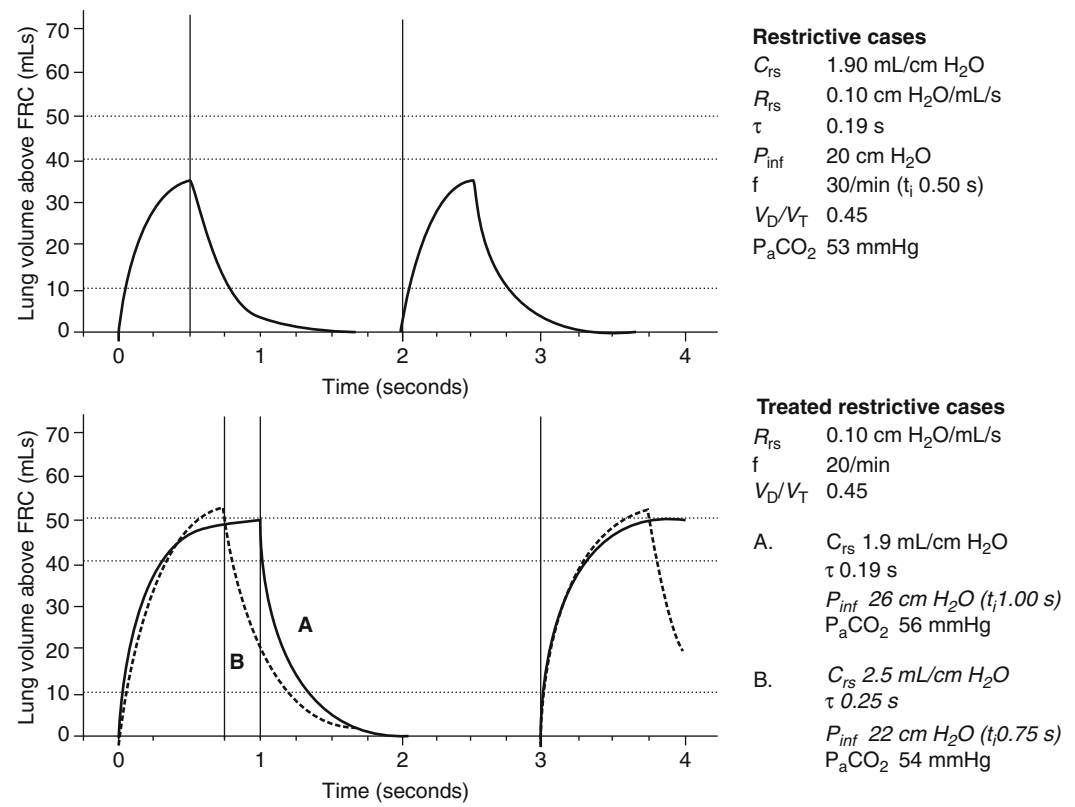


Fig. 50.7 Calculated inflation and deflation curves for “restrictive” bronchiolitis and theoretical response to changes in lung function. The nomenclature and assumptions are the same as Fig. 50.3. The “restrictive” cases are

the 10 selected cases reported by Hammer et al. (1997). See text for details. The definitions of curves **A** and **B** are shown in the column

50.6.1 Permissive Hypercapnia

Permissive hypercapnia has been suggested as a lung protective strategy for adults with ARDS. The strategy allows for a degree of hypercapnia provided the arterial pH does not fall below a pre-set minimum value; it may be used in combination with a degree of permissive hypoxemia with SpO₂ ~88 % in order to minimize mean airway pressure and hence barotrauma. Reda et al. (1997) reviewed their experience of this strategy in 29 infants with RSV bronchiolitis and reported significantly less barotrauma and shorter duration of MV and hospital stay. In contrast, Tibby et al. (1999) had a different experience in their 28 infants. They could achieve the strategy – as demonstrated by mean P_aCO_2 7.6 kPa (57 mmHg), mean pH 7.34, and maximal peak inspiratory pressure 25 cm H₂O – but it did not result in

improved survival, less barotrauma, or less nosocomial infection, when compared with their experience before using this strategy. Furthermore, the duration of MV was longer, although not statistically significant. The authors concluded that since they could not show a benefit of permissive hypercapnia, a prospective randomized controlled trial is needed. These reports are over 10 years old, and it is likely that equipoise is now lost. Most attendants incorporate a version of permissive hypercapnia in conventional MV for bronchiolitis (see Sect. 50.5.1). Again, it comes down to the mechanical cost of trying to achieve normal P_aCO_2 and the benefit of permitting higher values so that reduced ventilator settings can be applied.

Figure 50.7 uses the same nomenclature as Fig. 50.3. The figure uses the mean data of “restrictive” patients reported by Hammer et al. (1997). The upper panel shows that MV with a

rate of 30 breaths/min (t_i 0.50 s) and P_{inf} 20 cm H₂O would result in $P_a\text{CO}_2$ ~50 mmHg. Graphs A and B show that there is little or no effect on $P_a\text{CO}_2$ with a variety of theoretical manipulations in P_{inf} or C_{rs} . In comparison with “obstructive” patients and “controls,” FRC is low (Hammer et al. 1997). The implication of Fig. 50.7 is that recruitment of lung volume with consequent fall in C_{rs} should be the initial strategy.

50.6.2 High-Frequency Oscillatory Ventilation

High V_T and minute ventilation during MV result in high peak airway pressures and risk of air leak, as well as the necessity to use neuromuscular blockade. HFOV has been described as a rescue intervention for severe cases of RSV bronchiolitis since it may reduce these risks (Thompson et al. 1995; Medbo et al. 1997; Duval et al. 1999; Kneyber et al. 2005).

In a large multicenter review of HFOV, 18 of 27 patients with RSV infection had a successful response and were weaned to conventional MV (Arnold et al. 2000). Interestingly, the authors found that infants with RSV had significantly longer periods on HFOV compared with those with other causes of lower airway disease (10.5 vs 6.8 days). Recently, however, Berner et al. (2008) reported much shorter duration of HFOV (5.0 ± 1.6 days) in nine infants with RSV bronchiolitis (5.0 ± 1.6 days). The authors attributed this result to better $P_a\text{CO}_2$ control brought about by their practice of allowing infants to breathe spontaneously while on HFOV. This practice is used sometimes in neonatal care (Froese and Kinsella 2005). There are reasons why this approach is beneficial in infants. In children and adults, spontaneous breathing during HFOV leads to discomfort and distress which is probably due to the high level of imposed work of breathing (van Heerde et al. 2006a, b). In bench testing, with simulators, the level of imposed work of breathing in “patients” heavier than 25 kg exceeds normal physiologic work of breathing by ~200 % (van Heerde et al. 2006b). In contrast, simulations for infants weighing

3.5 kg show a low level of imposed work of breathing; hence, infants are able to tolerate spontaneous breathing during HFOV.

50.6.3 Extracorporeal Membrane Oxygenation

Despite maximal MV management, a small subgroup of infants with RSV bronchiolitis develop profound hypoxemia and a need for extracorporeal membrane oxygenation (ECMO). This form of support was first successfully applied to such infants in the period 1983–1988 (Steinhorn and Green 1990). Since then, it has been recognized as a potential alternative to MV for life-threatening RSV (Khan et al. 1995; Flamant et al. 2005). Steinhorn and Green (1990) reported that the need for ECMO during RSV bronchiolitis was observed mainly in previously premature infants, and their survival was 58 %. Khan et al. (1995) had a similar series, but only seven of their 24 cases had bronchopulmonary dysplasia – the survival rate was 96 %. Flamant et al. (2005) reported a survival rate of 70 % in a series of 14 cases.

This collected experience, over 20 years, raises two important questions. Why do some infants have such severe course of illness? Does our MV management make lung disease worse? It is beyond the scope of this chapter to review the literature on the biology of severity of RSV disease and genetic predisposition. Khan et al. (1995) and Flamant et al. (2005) suggest that bronchopulmonary dysplasia is an important risk factor. The question of whether attendants can make lung disease worse is also important and concerns us here. The series reported by Khan et al. (1995) was collected during 1989–1995, a time when HFOV was not in general use. This fact is reflected in the pre-ECMO summary measures of MV, which indicate high-pressure ventilation: mean peak inspiratory pressure 36 ± 5.5 cm H₂O (mean $\pm$ standard deviation), mean PEEP 5.8 ± 2.2 cm H₂O, and mean airway pressure 20 ± 4.7 cm H₂O. In addition, the normal pre-ECMO pH 7.43 ± 0.13 and $P_a\text{CO}_2$ 5.8 ± 2.1 kPa (44 ± 16 mmHg) suggest that the contemporary target for MV was normal gas exchange even at the cost of high MV pressures, rather than a more

permissive approach to hypercapnia that we would now accept (see also Sect. 50.6.1). Given that 96 % of these infants survived, the implication is that many such infants would not need ECMO where current standards are applied. The Flamant et al. (2005) supports this notion. This series was collected during 1996–2003 and 70 % of their ECMO cases had been on HFOV and 64 % had received inhaled nitric oxide before ECMO (see also Sect. 50.7.2). The authors do not provide any pre-ECMO pH or $P_a\text{CO}_2$ data for comparison.

50.7 Other Lung-Directed Therapies

There have been numerous clinical trials on treatments for bronchiolitis, such as bronchodilators, corticosteroids, and ribavirin (King et al. 2004). However, to date, little evidence exists for the effectiveness of any of these interventions. Most studies are underpowered and not of sufficient size or quality to rule out effectiveness. There is even less evidence in infants receiving these therapies during MV (Davison et al. 2004). In these cases, there is the added problem of clinical heterogeneity and lack of readily available bedside tools to classify or stratify severity. The illustrations in this chapter (see Figs. 50.3, 50.4, 50.5, and 50.7) indicate that targeting R_{rs} , or R_{rs} and C_{rs} together, should ease MV support. The question is whether these manipulations alter the time course of MV and PICU stay (outcomes often used in clinical trials). We have already discussed altering R_{rs} with bronchodilators (see Sect. 50.5.3). Another strategy that could be used to decrease R_{rs} is helium-oxygen gas mixture for ventilation. Also, we could use surfactant to increase C_{rs} . Last, we could use inhaled nitric oxide to match lung perfusion to ventilation, i.e., to reduce V_D/V_T . Each of these approaches is discussed.

50.7.1 Helium-Oxygen Gas Mixtures

Helium is an inert gas with a density that is one-seventh that of air. Carbon dioxide diffuses more

easily through helium than through air. Laminar flow in narrowed airways is more likely to be preserved when helium is used instead of air (Gupta and Cheifetz 2005). Taken together, helium and oxygen (heliox) mixtures should decrease resistance to gas flow and theoretically reduce the work of breathing in conditions where increased resistance plays a part.

In the early stage of RSV lower respiratory tract disease, the use of heliox has had varied effects. An early pilot study of 18 infants with bronchiolitis showed that after 20 min of heliox, there was a reduction in clinical score and a 1.8 % improvement in SpO_2 , although six infants went on to require CPAP (Hollman et al. 1998). A multicenter, randomized controlled trial in 39 non-intubated infants using a heliox mixture with 78 % helium within 8 h of admission to PICU showed no difference in the proportion that required MV (19 % controls vs 22 % heliox group) (Liet et al. 2005). A crossover study showed that 30 min of CPAP with or without 70 %:30 % helium-oxygen reduced clinical score and transcutaneous PCO_2 (Martinon-Torres et al. 2008). Patients receiving heliox nasal CPAP had a greater decrease in clinical score compared with air-oxygen nasal CPAP (2.12 vs 1.08 points) and a greater decrease in transcutaneous PCO_2 (9.7 vs 5.4 mmHg or 1.3 vs 0.7 kPa). Most recently, a Cochrane review of four quasi-trials involving 84 infants concluded: “the addition of heliox therapy may significantly reduce a clinical score evaluating respiratory distress in the first hour after starting treatment... nevertheless, there was no reduction in the rate of intubation, in the need for MV, or in the length of PICU stay” (Liet et al. 2010).

There is even less evidence for using heliox in MV cases of RSV bronchiolitis. Gross et al. (2000) studied 10 infants each given a sequence of heliox mixtures (50 %:50 %, 60 %:40 %, and 70 %:30 %) and found that increasingly higher doses failed to improve gas exchange. In contrast to these findings, Kneyber et al. (2009) studied 13 infants and found that R_{rs} was significantly decreased by MV with 60 %:40 % heliox, although this improvement was not accompanied by improved CO_2 elimination, decreased peak

expiratory flow rate, or decreased end-expiratory lung volume.

50.7.2 Surfactant Therapy

Endogenous surfactant activity can be impaired in the course of RSV disease for several reasons: (a) the virus-induced damage of type II pneumocytes results in a reduction of surfactant synthesis, (b) the protein-rich edema causes an inactivation of surfactant by specific inhibitors and plasma components, (c) damage to the alveolar-capillary membrane may cause loss of surfactant into the interstitium and blood, (d) MV with large V_T and high FiO_2 can deplete further or damage surfactant, and (e) lack or inactivity of surfactant favors bronchiolar and alveolar collapse and lung permeability to macromolecules (Luchetti et al. 2002).

The theoretical rationale for using surfactant treatment in RSV bronchiolitis is to restore the surfactant pool, so that while MV with PEEP recruits alveoli, surfactant may stabilize them, maintain their patency, and thus restore ventilation of non-ventilated regions of the lung. It should improve lung compliance. A Cochrane review of three trials (Luchetti et al. 1998, 2002; Tibby et al. 2000) of natural surfactant in bronchiolitis demonstrates a trend towards a decrease in the duration of ventilatory support (mean 2.6 days, $P=0.07$) and a decrease in PICU stay (mean 3.3 days, $P=0.04$) without adverse effects, but only 79 infants were included in the review (Ventre et al. 2006).

50.7.3 Inhaled Nitric Oxide

Inhaled nitric oxide may improve oxygenation in certain infants with RSV bronchiolitis, but it does not appear to have any overall benefit in groups of patients (Patel et al. 1999). It does not function as a bronchodilator, and no studies have looked at its effect on V_D/V_T . In the wider context of treatment during acute hypoxemic respiratory failure, it does result in improvement in oxygenation, but there is no improvement in outcome (Dobyns et al. 1999).

Future Perspectives

Viral bronchiolitis accounts for almost 10 % of PICU admissions in the UK, some 1,000 infants per year (O'Donnell et al. 2010); perhaps it is time to get the evidence for how best to manage such patients. For example:

- How do we decide when to intervene with noninvasive support?
- Does noninvasive support limit the progression in worsening lung mechanics?
- Can we better characterize the clinical phenotypes of “bronchiolitis” requiring conventional MV using widely available techniques?
- Can we standardize MV settings according to clinical phenotype and lung function parameters?
- Can the intrapulmonary consequences of bronchiolitis (e.g., ventilation-perfusion inequalities and shunt, raised V_D/V_T , increased resistance, decreased compliance, prolonged time constant) be targeted by specific therapies?

Essentials to Remember

Respiratory support of infants with bronchiolitis is complicated, and we have the potential for making a patient worse after endotracheal intubation if we do not pay attention to the interaction between lung mechanics and the time course of mechanical ventilation. The essential points to remember are:

- The progression in deteriorating pulmonary mechanics is decrease in respiratory system compliance (“bronchiolitis”), followed by combined decrease in respiratory system compliance and increase in respiratory system resistance (“obstructive”), followed by a state where low lung volume and very low respiratory system compliance predominate (“restrictive”).
- The acute deterioration in pulmonary mechanics – bronchiolitis and obstructive – is accompanied by increased dead

space-to-tidal volume ratio and pulmonary ventilation-perfusion inequalities.

- Before endotracheal intubation, the aim of respiratory support is to overcome the exaggerated work of breathing and abnormal lung mechanics and allow for resolution of the primary pathophysiology. Various forms of noninvasive CPAP have a role.
- After endotracheal intubation, each phase of the condition – bronchiolitis, obstructive, and restrictive – requires different strategies. In the acute phase, focus on the time course of lung inflation, respiratory system resistance, and the pulmonary time constant for deflation will limit overinflation and dynamic hyperinflation. Read the whole chapter for more details!

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Christopher L. Carroll

Educational Goals

- To review the changes in pulmonary mechanics that occur in children with severe asthma exacerbations
- To review strategies for the use of non-invasive and invasive positive pressure in this population
- To review therapeutic interventions for severe asthma exacerbations and the complications associated with these therapies

51.1 Introduction

After increasing for decades, the prevalence of asthma in the USA appears to have stabilized, and there is evidence that the rates of asthma hospitalizations have begun to decrease in children. However, the worldwide medical and economic burden of asthma remains high. Asthma remains one of the leading causes of chronic illness in children. Acute asthma exacerbations are a major public health problem, resulting in significant financial costs, reduced quality of life, and time lost from school for the child and from work for the parent. Most children with an acute exacerbation will respond to outpatient management. However, a significant subset will

require more intensive therapy, inpatient hospitalization, and potentially endotracheal intubation and mechanical ventilation (Schramm and Carroll 2009; Biarent 2001; Werner 2001; Phipps and Garrard 2003; Papiris et al. 2002; Roberts et al. 2002; Pendergraft et al. 2004).

Mechanically ventilated children with acute asthma are some of the most challenging patients to manage in the pediatric intensive care unit (ICU), requiring frequent reassessment of pulmonary mechanics and close monitoring for potentially life-threatening complications (Schramm and Carroll 2009; Biarent 2001; Werner 2001; Phipps and Garrard 2003; Papiris et al. 2002; Roberts et al. 2002; Pendergraft et al. 2004). Although potentially lifesaving, endotracheal intubation and mechanical ventilation carry significant risk in children with asthma. The presence of an endotracheal tube can aggravate a child's bronchospasm and is associated with a high incidence of serious complications in children with asthma (25–50 %) (Cox et al. 1991). In addition, modest degrees of respiratory distress and hypercarbia are generally well tolerated in non-intubated children with severe asthma (Roberts et al. 2002). Therefore, prevention of endotracheal intubation and mechanical ventilation is the first goal of inpatient therapy. However, there are instances when the risks of potential respiratory failure outweigh the potential complications of intubation and mechanical ventilation. These factors will be outlined in this chapter, and when possible, evidence-based recommendations will be provided.

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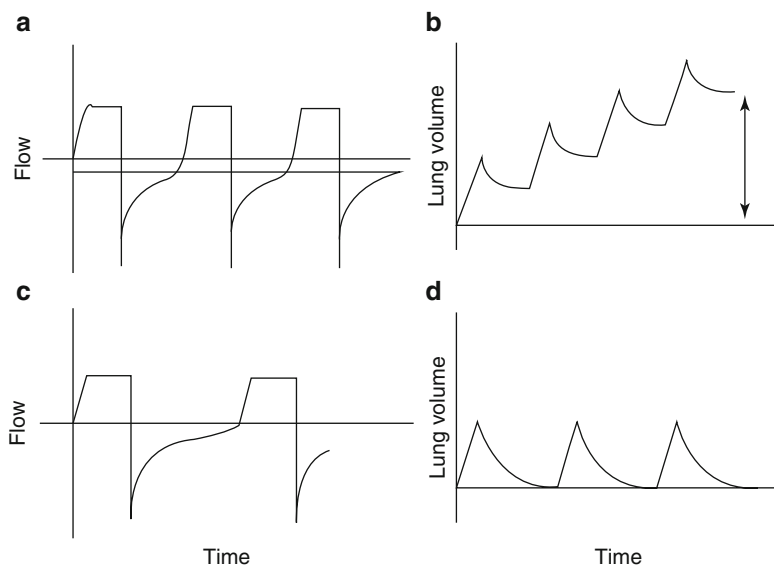


Fig. 51.1 Mechanics of dynamic hyperinflation in acute severe asthma (Rotta and Steinhorn 2007). **(a)** A flow-time curve shows that inspiration begins before complete exhalation of the previous breath, leading to gas trapping (shaded area). **(b)** Gas trapping over the course of several breaths leads to an increased end-expiratory lung volume. The trapped volume over functional residual capacity is

indicated by the *double-headed arrow*. **(c)** Increase in expiratory time and decrease in respiratory rate allow for complete exhalation prior to initiation of the next breath. **(d)** Increase in expiratory time and decrease in respiratory rate result in no air trapping and absence of dynamic hyperinflation

51.2 Severity Assessment

51.2.1 Changes in Pulmonary Mechanics

Changes in pulmonary mechanics that occur during acute asthma can be severe and life-threatening, leading to impaired gas exchange, respiratory muscle fatigue, and eventually to respiratory failure (Oddo et al. 2006; Stather and Stewart 2005). Airway inflammation, smooth muscle-mediated bronchoconstriction, and intraluminal mucous plugging lead in turn to acute increases in airway resistance, pulmonary hyperinflation, and physiologic dead space (Oddo et al. 2006; Stather and Stewart 2005). Understanding these pathophysiologic changes is crucial when attempting to manipulate pulmonary mechanics with invasive and noninvasive positive pressure.

During acute asthma, increased airway inflammation and bronchoconstriction lead to increased airway resistance and a prolongation of expiratory time constants. Lower pulmonary elastic recoil

asthma in children with asthma also contributes to a low driving force for expiration. The combination of these factors and the premature closure of inflamed airways during exhalation lead to dynamic hyperinflation and an increased positive end-expiratory pressure at the alveolar level (auto-PEEP) (Oddo et al. 2006; Stather and Stewart 2005). Because alveolar pressure must be reduced to subatmospheric levels to initiate the next breath, auto-PEEP increases the inspiratory load and can induce respiratory muscle fatigue. The initial physiologic response to this pathophysiology is tachypnea with a resultant increase in minute ventilation and hypocapnia. However, in the setting of airflow obstruction, this increased minute ventilation leads to incomplete exhalation, air trapping and dynamic hyperinflation (Fig. 51.1) (Rotta and Steinhorn 2007). Elevation in intrathoracic pressure from this dynamic hyperinflation can lead to barotrauma and hemodynamic compromise from impaired preload.

Additionally, during severe exacerbations, the normally passive process of exhalation becomes

active in an attempt by the patient to force the inspired gas out of the lungs. High airway resistance and hyperinflation also increases the inspiratory work during inhalation. This sustained functioning of the respiratory muscles leads to increased metabolic demand and can lead to respiratory muscle fatigue over time (Oddo et al. 2006; Stather and Stewart 2005; Rotta and Steinhorn 2007). Respiratory failure can occur if ventilatory demand exceeds the work output of the respiratory muscles.

51.2.2 Assessment of Children with Acute Asthma

Accurately assessing a child's degree of respiratory impairment is often difficult during acute exacerbations (Werner 2001; Phipps and Garrard 2003; Papiris et al. 2002; van der Windt et al. 1994). Due to their age and developmental level, acutely ill children are frequently unable to reliably and reproducibly perform tests that are used to assess severity of illness in adult patients with asthma (van der Windt et al. 1994). Spirometry and peak flow testing are generally not useful in most critically ill children (van der Windt et al. 1994; National Heart, Lung and Blood Institute. Asthma Education and Prevention Program 2007). In this population, a combination of subjective and objective parameters is best used to qualify the degree of distress (National Heart, Lung and Blood Institute. Asthma Education and Prevention Program 2007). Symptoms such as breathlessness, level of alertness, and ability to speak and physical signs such as respiratory rate, use of accessory muscles, degree of wheezing, and heart rate can provide important indicators as to the severity of a child's exacerbation. Locally, many institutions use a clinical asthma score to quantify these objective and subjective findings (Keogh et al. 2001). These scores are used to facilitate communication between providers and to guide therapeutic interventions.

Blood gas measurements are also frequently used to assess respiratory function in this population; however, blood gas analysis has been

shown not to correlate with acute asthma severity or to predict respiratory failure (Gentile et al. 2003). If the child is responding to therapy, hypercarbia alone is not an indication for intubation. Clinical judgment is crucial, since modest degrees of hypercarbia are generally well tolerated in non-intubated children with acute asthma and many children presenting with hypercarbia do not require intubation (Roberts et al. 2002). Conversely, however, a normal or rising carbon dioxide level can indicate impending respiratory failure in a child with significantly increased work of breathing and airflow obstruction.

Assessment of oxygen saturation should be performed on all children with an acute exacerbation. Compared to adults with acute asthma, children are significantly more likely to require oxygen therapy during an exacerbation. In addition, hypoxemia is an important indicator of impending respiratory failure in children with asthma (Werner 2001).

Determining which child will benefit from intubation can be challenging. The clinician must weigh the probability of improvement with therapy, the potential for respiratory arrest, and the potential complications of intubation and mechanical ventilation. However, there are some absolute indications for the intubation of a child with acute asthma. These include respiratory or cardiac arrest, severe hypoxia, or a rapid deterioration of mental status (Schramm and Carroll 2009; Biarent 2001; Werner 2001). Progressive exhaustion despite aggressive treatment is another indication for intubation; however, this finding is subjective and can be difficult to judge in young children. Other potential indications for intubation can be found in Table 51.1.

In adults with asthma, certain populations have been identified that may be more likely to develop respiratory failure. In the meta-analysis by Alvarez of studies in asthmatic adults (Alvarez et al. 2005), a previous history of hospital admission and ICU admission or previous intubation for asthma was associated with an increased likelihood of mechanical ventilation. In children, the risks are less clear. A "brittle" or acute asphyxial asthma phenotype has been proposed, in which there is a brief duration of symptoms and a rapid

Table 51.1 Indications for endotracheal intubation

Inability to speak or absent breath sounds
Poor aeration with absent wheezing
Paradoxical thoracoabdominal movement
Rising PaCO ₂
Hypoxemia (PaO ₂ < 60 mmHg) with deteriorating clinical status
Altered level of consciousness (agitation, confusion, or drowsiness)
Hemodynamic instability (hypotension or bradycardia)
Respiratory or cardiac arrest

PaCO₂ partial pressure of carbon dioxide in arterial blood,
PaO₂ partial pressure of oxygen in arterial blood

progression to respiratory failure (Maffei et al. 2004). Response to therapy tends to be rapid and duration of mechanical ventilation short. However, others have questioned the existence of this phenotype. There are significant regional differences in the incidence of intubation and mechanical ventilation for acute asthma, ranging from 9 to 38 % in some reviews (Bratton et al. 2005). These variations suggest that provider preference and local practice have significant influence on the decision to intubate. In addition, other non-patient-related factors, such as distance from a children’s hospital, may impact whether a child is intubated.

51.3 Noninvasive Respiratory Support

Noninvasive positive pressure ventilation (NPPV) is a promising therapy for the treatment of a variety of respiratory diseases in children, including asthma (Thill et al. 2004; Carroll and Schramm 2006a; Beers et al. 2007; Soroksky et al. 2003). NPPV provides positive airway pressure via a nasal mask or a nasal-oral face mask. The positive pressure is delivered either continuously or in a bi-level mode that varies between higher inspiratory and lower end-expiratory pressures (Meduri et al. 1996; Ram et al. 2005). During acute asthma exacerbations, NPPV works by helping to avoid airway collapse during exhalation and by reducing the change in alveolar pressure needed to initiate inspiration, thereby

unloading fatigued respiratory muscles and improving dyspnea. In addition, in bi-level positive airway pressure modes, the inspiratory pressure helps to improve tidal volumes, further supporting a child’s respiratory function and improving gas exchange. NPPV also preserves a child’s natural airway and airway clearance, potentially avoiding some of the complications associated with invasive ventilation and with the sedation needed to provide invasive ventilation.

Although NPPV is used with increasing frequency for the treatment of acute asthma, its utility remains controversial. Recent reviews by the Cochrane Collaboration have concluded that NPPV has not been shown to improve outcomes in adults with asthma (Ram et al. 2005). However, at least in children, early intervention with NPPV in acute severe asthma may improve outcomes and may potentially prevent endotracheal intubation (Thill et al. 2004; Carroll and Schramm 2006a; Beers et al. 2007). Several small pediatric case series have been performed, and although the sample size in each of these studies is small, each found an improvement in gas exchange and respiratory effort in children with acute severe asthma. In addition, the use of NPPV was generally well tolerated in these populations, with children requiring little or no sedation and having few adverse events. However, careful patient selection, staff familiarity with NPPV, and close monitoring of the patient were reported as important for the success of this intervention.

When using NPPV in children, providers need to be concerned about several patient-related factors. These include the challenges of finding an appropriate-sized mask as well as the prevention of gastric distention and skin breakdown. Due to the wide variation in the sizes of children, standard-sized nasal and nasal-oral masks may not fit a particular child. Nasal masks are usually best tolerated but are more prone to air leaks and therefore may not be able to deliver positive pressure reliably in uncooperative children. The use of nasal-oral masks may improve gas exchange but increase the risk of gastric distention, a common effect of NPPV. In children, gastric distention is of particular concern since an immature gastroesophageal sphincter will increase a child’s

risk of vomiting and aspiration. Skin abrasions and ulcerations can occur from the pressure required to secure the mask to the child's face. Close assessment of the patient's skin for breakdown is important, particularly with long-term use of NPPV. There is anecdotal evidence that skin breakdown may be diminished or prevented by the prophylactic use of protective skin coverings. Whenever possible, short breaks (10–15 min every 4 h) should be taken off NPPV in order to provide relief to the skin, to assess for skin breakdown, and to reposition the mask.

51.4 Invasive Mechanical Ventilation

51.4.1 Strategies for Intubation

Rapid sequence intubation technique is the preferred method of intubation in children with acute asthma. Prior to intubation, the child should be preoxygenated with 100 % oxygen, placed on respiratory and cardiac monitors, suctioned if necessary, and the stomach decompressed. Ketamine is a preferred induction agent due to its bronchodilatory effects. Atropine may also be used as an antisialagogue and to reduce the incidence of vagal-induced bradycardia. Short-acting neuromuscular blocking agents should be considered to reduce some of the large swings in airway pressure following intubation and possibly prevent peri-intubation barotrauma and its resultant complications. The Sellick maneuver (i.e., the application of cricoid pressure during intubation) should be used to reduce the risk of aspiration. Primary (via visualization and auscultation) and secondary (end-tidal CO₂ monitoring and chest radiography) methods of confirming endotracheal tube placement are essential.

51.4.2 Strategies for Mechanical Ventilation

The primary goals of mechanical ventilation during acute asthma exacerbations are to achieve adequate oxygenation and ventilation while

minimizing iatrogenic hyperinflation and levels of intrathoracic pressure that could negatively impact cardiac output (Bohn and KIssoon 2001). Several strategies have been proposed to achieve these goals. However, most are based on expert reviews or small retrospective cohorts (Koh 2001; Darioli and Perret 1984; Sarnaik et al. 2004; Malmstrom et al. 2001; Shugg et al. 1990). There are no large-scale studies comparing mechanical ventilation strategies in this population. In the end, like most of pediatric critical care, in the absence of evidence-based medicine, the treatment of acute asthma and respiratory failure involves primarily phronesis (practical wisdom): a customized decision for an individual patient (Tobin 2008).

However, there are several key themes in the ventilation of children with acute asthma and respiratory failure that are generally accepted. Controlled hypoventilation with low peak inspiratory pressures, low respiratory rates, and permissive hypercapnia is often used with the perception that this strategy improves outcomes and decreases complications (Darioli and Perret 1984; Sarnaik et al. 2004). Plateau pressures of less than 30 cm H₂O and tidal volumes of less than 8 mL/kg are suggested to reduce the potential for barotrauma (Levy et al. 1998). These lower pressures and volumes also may reduce iatrogenic increases in intrathoracic pressure that may significantly impair preload and cardiac output. A strategy of lower respiratory rates may allow adequate expiratory time to accommodate for delayed time constants and also reduce iatrogenic dynamic hyperinflation. However, in acute asthma, a child's lung has heterogeneous areas with varying degrees of obstruction. As a result, during mechanical ventilation a child may not be able to reach a complete expiratory volume. However, a clinician may be able to provide sufficient emptying to prevent most dynamic hyperinflation while balancing the need to provide some degree of ventilation. A strategy of permissive hypercapnia with buffering of pH (goal >7.2) is used in these cases. When possible, spontaneous respiration should also be used to allow a child to regulate their own respiratory rate and expiratory time. However, practically in children,

difficulty with providing sedation may preclude support modes without set respiratory rates.

Both pressure-limited and volume-limited modes have been used to ventilate children with acute asthma and respiratory failure, but neither approach has been demonstrated to be more effective than the other (Sarnaik et al. 2004; Malmstrom et al. 2001). However, there are important advantages and disadvantages of each therapy to consider when the clinician weighs the decision about which mode to use in a particular patient. Pressure-limited modes provide decelerating gas flow with a preset peak inspiratory pressure and an inspiratory tidal volume that will vary based on changes in compliance and resistance. This has the theoretical advantage of limiting hyperinflation in this population; however, high levels of airway resistance may limit effective tidal volumes, and sudden changes in resistance with acute bronchospasm can cause significant variation in delivered tidal volume. Volume-limited modes will provide a more constant tidal volume and may provide for more consistent delivery of aerosolized medications. However, due to the heterogeneous nature of the lung in acute asthma, there may be overdistention and air trapping in areas with less airway obstruction. Volume-limited modes also have the advantage of allowing the clinician to assess for changes in resistance and dynamic and static compliance by assessing changes in peak and plateau pressures over time. Response to therapy can therefore be quantified by examining for any decrease in the difference between peak and plateau pressures that will reflect improving resistance. Newer, pressure-regulated volume control modes can provide a guaranteed tidal volume with a decelerating gas flow and combine some of the advantages of both pressure-limited (preset peak pressure) and volume-limited ventilations (consistent minute ventilation). These modes may be advantageous in children with acute asthma, but clinical trials are needed.

The use of external PEEP in patients with acute asthma and respiratory failure has been controversial. External PEEP may further increase air trapping and dynamic hyperinflation, factors that have been associated with increased

complications of mechanical ventilation (Tuxen and Lane 1987). For these reasons, some authors continue to advocate no external PEEP (Oddo et al. 2006). Other authors, however, advocate an extrinsic PEEP to match intrinsic auto-PEEP, theorizing that some external PEEP minimizes atelectasis and helps to maintain patent airways to facilitate mucous clearance in this population. In practice, the potential beneficial effects of external PEEP must be balanced with the potential negative effects of external PEEP in a particular patient.

51.5 Use of Inhalational Gases

51.5.1 Heliox

Heliox, a blend of helium and oxygen, reduces airway resistance by converting density-dependent turbulent airflow within the airways to a more laminar flow (Barach 1935). As such, heliox is an attractive therapy for children with severe asthma, potentially reducing work of breathing, increasing nebulized drug delivery, and improving gas exchange to the distal airways. Small studies in children have found a reduction in dyspnea, improved gas exchange, and improved pulmonary function in some patients. However, these beneficial effects are most apparent within the first hour of therapy, after which most conventionally treated children improve similarly. In addition, a recent systematic review of the literature failed to demonstrate a significant beneficial effect for the treatment of acute asthma in children (Ho et al. 2003). However, helium is a biologically inert gas, and heliox has no known adverse effects. With this risk/benefit profile, a brief trial of heliox seems warranted in select children with severe asthma. If the child does not rapidly improve with this therapy, the heliox should be discontinued and other therapies considered. Clinicians need to be aware, however, that to significantly lower the density of the inhaled gas, helium needs to comprise 60–80 % of the mixture. Significantly hypoxemic children who require greater than 40 % inspired oxygen should therefore not be considered for this therapy.

51.5.2 Inhalational Anesthetics

Volatile inhalational anesthetics are potent bronchodilators and have been used to treat severe refractory exacerbations in both adults and children (Maltais et al. 1994; Shankar et al. 2006). Although their mechanism of action has not been established, some of the proposed mechanisms include direct relaxation of bronchial smooth muscles, β_2 -adrenergic receptor stimulation, and inhibition of hypercapnic bronchoconstriction (Maltais et al. 1994; Shankar et al. 2006). Because of the novelty of these proposed therapeutic mechanisms, inhalational anesthetics may be particularly useful for the treatment of acute asthma that is refractory to conventional bronchodilators. Halothane, isoflurane, and sevoflurane have each been reported to be beneficial (Maltais et al. 1994; Shankar et al. 2006). As with heliox therapy, the beneficial effects of these inhalation anesthetics typically occur rapidly. But unlike heliox, the effects may be sustained (Shankar et al. 2006).

Side effects from the inhalation anesthetics include cardiac arrhythmias and hypotension. The hypotension is dose-dependent and due to vasodilation and direct myocardial depression. In addition, there is the practical problem of delivering these agents in the ICU. Many ventilators used in the ICU are unable to scavenge these agents, requiring children to be ventilated in the operating room setting and potentially with a less sophisticated ventilator. The clinician, therefore, needs to weigh the potential risks of changing ventilators and/or locations with the potential benefits of this therapy. As a result, inhalation anesthetics are generally reserved for severely ill patients, refractory to maximal conventional bronchodilators.

51.6 Pharmacologic Treatment

First-line care for the treatment of pediatric asthma exacerbations includes oxygen, systemic corticosteroids, and aerosolized β_2 -agonists such as albuterol (Schramm and Carroll 2009; Biarent 2001; Werner 2001; Phipps and Garrard 2003;

Papiris et al. 2002; Roberts et al. 2002; Pendergraft et al. 2004). Children with severe exacerbations, unresponsive to these treatments, are typically admitted to a pediatric ICU for a close monitoring of their respiratory status. Several second-line therapies are available, such as intravenous β_2 -adrenergic receptor agonists, anticholinergics, magnesium, and methylxanthines. Treatment of severe asthma in children is frequently subjective and includes a combination of therapies (Schramm and Carroll 2009; Biarent 2001; Werner 2001; Phipps and Garrard 2003; Papiris et al. 2002; Roberts et al. 2002; Pendergraft et al. 2004). Few controlled studies exist that examine the efficacy of treatments received in the pediatric intensive care unit, and as a result, there are few evidence-based treatment strategies.

51.6.1 β_2 -Adrenergic Receptor Agonists

β_2 -adrenergic receptor agonists reduce smooth muscle-mediated bronchoconstriction, and higher doses of β_2 -adrenergic receptor agonists therapy, delivered either by aerosol or intravenously, are frequently the next step in the treatment of severe asthma in children. Continuously delivered albuterol is generally preferred in children and has been found to reduce hospitalizations and improve pulmonary function when compared to intermittent aerosol treatments (Camargo Jr et al. 2003). Relatively high doses of continuous albuterol (20–30 mg/h) are routinely used to treat acute bronchospasm in children, and undiluted albuterol aerosols have even been used in certain clinical situations to reduce the time required for treatment in the emergency department setting (Gutglass et al. 2000). In children with severe airway obstruction, intravenous β_2 -adrenergic receptor agonists are sometimes used to overcome problems with aerosolized drug delivery. Terbutaline, currently the only intravenous β_2 -adrenergic receptor agonists available in the USA, has been shown to improve pulmonary function and gas exchange and to shorten length of stay when titrated according to clinical asthma

score (Carroll and Schramm 2006b). Despite previous evidence that the use of intravenous terbutaline was not associated with cardiac injury (Chiang et al. 2000), there is some recent concern that the chronotropic effects of β_2 -adrenergic receptor agonists therapies may lead to occult myocardial injury from impaired coronary perfusion and increased oxygen consumption. This effect may be worsened in dehydrated patients with inadequate intravascular volume.

51.6.2 Anticholinergics

Anticholinergic medications block acetylcholine action at the muscarinic receptors of the airway smooth muscle, thereby reducing smooth muscle-mediated bronchoconstriction by a different mechanism than β_2 -adrenergic receptor agonist therapy. Aerosolized anticholinergics, such as ipratropium, are effective bronchodilators in children with asthma. Used in the emergency department setting, the early administration of aerosolized anticholinergic agents with β_2 -adrenergic receptor agonists improves pulmonary function and reduces hospitalization for acute asthma by 30 % (Rodrigo and Castro-Rodriguez 2005). This improvement is thought to be more pronounced in more acutely ill children. However, during severe acute exacerbations, the continued use of aerosolized anticholinergic therapy in hospitalized patients has not been shown to improve outcomes or to shorten duration of illness. But given the limited toxicity of this medication and its potentially synergistic effects with β_2 -adrenergic receptor agonist therapy, a trial of aerosolized anticholinergic therapy should be considered in children with severe asthma.

51.6.3 Corticosteroids

Corticosteroid treatment reduces the underlying inflammatory process in acute asthma. In the USA, the National Asthma Education and Prevention Program Guidelines recommend a dose of up to 2 mg/kg/day during acute

exacerbations (National Heart, Lung and Blood Institute. Asthma Education and Prevention Program 2007). However, these guidelines do not offer a recommended corticosteroid dose during severe exacerbations. For children in impending respiratory failure, there is little published evidence regarding corticosteroid dose and duration. Some experts report recommended doses significantly higher than the national guidelines for less severe exacerbations and as 4 mg/kg/day of systemic prednisone or methylprednisolone (Werner 2001; Warner and Naspitz 1998). In addition, although oral corticosteroids are as beneficial as intravenous for less severely ill children, intravenous corticosteroids may be preferred in the critically ill. In this population, high doses of β_2 -adrenergic receptor agonist therapy may cause nausea, vomiting, and impaired gastrointestinal absorption, thereby necessitating intravenous corticosteroid therapy.

51.6.4 Magnesium

Magnesium, when delivered intravenously, is a potent bronchodilator that relaxes bronchial smooth muscle and may also reduce the inflammatory response during acute asthma (Rowe and Camargo 2008). Similarly to aerosolized anticholinergic therapy, the use of intravenous magnesium improves pulmonary function and reduces hospitalization when given the children with acute exacerbations in the emergency department setting. However, the continued use of intravenous magnesium in hospitalized patients has not been shown to improve outcomes. Side effects from this treatment, such as flushing, fatigue and pain at the injection site, are rare. Aerosolized magnesium therapy has not been shown to be an effective treatment for acute asthma.

51.6.5 Methylxanthines

Aminophylline and theophylline were at one time the primary therapy for acute asthma

exacerbations. Recently, these medications have fallen out of favor due to their narrow therapeutic range, higher incidence of side effects, and decreased effectiveness compared to sympathomimetic therapy (McFadden 2003). However, in the population of children with severe asthma and respiratory failure, methylxanthines may continue to play a role in those children incompletely responsive to other bronchodilator therapies.

51.7 Complications and Complication Management

Although mechanical ventilation may be a life-saving treatment for respiratory failure due to severe asthma exacerbations, the complications due to the endotracheal intubation and mechanical ventilation can be significant. In non-intubated children with severe exacerbations, the incidence of complications is relatively small (<3 %). However, intubated children are 15 times more likely than non-intubated children to experience a complication during their treatment (Carroll and Zucker 2007). In addition, children experiencing a complication have significantly longer hospital costs and lengths of stays. The most effective way to avoid these complications is to prevent intubation. However, prevention of respiratory failure is not always possible in this population.

51.7.1 Complications Associated with Endotracheal Intubation

More than half of all complications occurring in asthmatic patients undergoing mechanical ventilation occur during or immediately after intubation (Table 51.2) (Werner 2001). Desaturation can be sudden and severe and can occur even with preoxygenation. Bradycardia can occur from either the desaturation or from vagal reflexes induced by laryngoscopy. Preoxygenation and pretreatment with atropine may reduce the risk of bradycardia. Hypotension can occur immediately

following intubation, due to the sudden increase in intrathoracic pressure and impaired preload. The clinician should assess a child's intravascular volume prior to intubation and consider whether the child requires fluid resuscitation to augment preload. Gastric distention from the use of NPPV or the presence of stomach contents increases the risk of vomiting and aspiration in this population, so the stomach should be decompressed. Finally, the presence of an endotracheal tube itself may also aggravate bronchospasm. Providers should be prepared for an acute worsening of bronchospasm immediately following intubation.

Complications surrounding the intubation of a child with asthma can be severe and life-threatening. Prolonged attempts at intubation by inexperienced providers can increase these risks. In addition, children with asthma are more likely to be intubated either in the field by emergency medical providers or at a community hospital by providers not trained in the treatment of children. This practice may increase the risk of complications in these children. However, even with the most experienced providers, children with respiratory failure and asthma are an unstable population, prone to complications due to their underlying pathophysiology. Providers need to be vigilant in their assessment for these complications surrounding intubation.

51.7.2 Complications Associated with Mechanical Ventilation

Complications associated with mechanical ventilation can occur either from the positive pressure ventilation or from the other therapies required to facilitate the mechanical ventilation (Table 51.2). Positive pressure ventilation, delivered either invasively or noninvasively, can significantly increase dynamic hyperinflation and raise intrathoracic pressure during severe asthma exacerbations, having potentially severe effects on hemodynamics and respiratory status. During mechanical ventilation, insufficient exhalation times may further worsen this dynamic hyperinflation.

Table 51.2 Complications

<i>Associated with endotracheal intubation</i>
Desaturation
Bradycardia
Hypotension
Aspiration pneumonia
<i>Associated with positive pressure and mechanical ventilation</i>
Pneumomediastinum
Pneumothorax
Hypotension
Arrhythmia
Ventilator-associated pneumonia
Rhabdomyolysis
Endotracheal tube displacement

Barotrauma, or the development of an extra-pulmonary air leak such as a pneumothorax or pneumomediastinum, is caused by dynamic hyperinflation and is one of the most commonly reported complication in severe asthma, occurring in 14–27 % of intubated asthmatics (Shugg et al. 1990; Carroll and Zucker 2008). Positive pressure of any type (via endotracheal intubation or NPPV) will significantly increase a child's risk of developing barotrauma. However, although barotrauma should be avoided if possible, supporting the oxygenation and ventilation of a child in respiratory failure is paramount to avoiding barotrauma. Pneumothoraces, if significant, should be treated with thoracentesis and placement of a chest tube. Pneumomediastina and subcutaneous emphysema do not require treatment.

Dynamic hyperinflation and a resultant elevation in intrathoracic pressure lead to impaired venous return and hypotension. In addition, many of the therapies given for acute bronchospasm are also chronotropic, decreasing diastolic filling time and further impairing cardiac output. Although routine volume resuscitation is not recommended in adults, children with acute severe asthma are frequently at least moderately dehydrated on presentation due to increased insensible losses and poor oral intake. Children typically benefit from some degree of hydration. This is usually intravenous in children with severe exacerbations.

In addition, bronchospasm can be worsened by inadequate sedation and analgesia during mechanical ventilation. Due to their age and developmental level, it is sometimes difficult in children to achieve adequate sedation levels that allow spontaneous breathing without significantly depressing respiration. Inadequate sedation can lead to complications such as aspiration pneumonia and endotracheal tube displacement. As a result, children may require deep sedation and sometimes muscle relaxation to facilitate mechanical ventilation. The use of neuromuscular blockade in this population has been linked to the development of rhabdomyolysis, another frequent complication of mechanical ventilation for asthma that has been reported in 18–38 % of all adults intubated for severe exacerbations (Shugg et al. 1990).

Conclusions

Children mechanically ventilated for asthma are among the most challenging patients to manage in the pediatric ICU. Increased airway resistance, dynamic hyperinflation, and mucous production each contribute to alterations in pulmonary mechanics that can change widely and rapidly during a child's hospitalization. The main goals of mechanical ventilation are to balance amounts of oxygenation and ventilation with the desire to prevent further hyperinflation. Generally, a strategy of controlled hypoventilation, with low respiratory rate and longer exhalation times, is used. Extrinsic PEEP is generally set to match the intrinsic auto-PEEP of the patient. The treatment of children with acute asthma and respiratory failure can be associated with significant morbidity, both from the disease and from the treatments received. Children mechanically ventilated for asthma require close monitoring for sudden changes in pulmonary mechanics that may impact ventilatory support and for gas exchange and for complications of mechanical ventilation. Optimal care for these children requires a careful assessment of each child's condition and a thorough understanding of the child's underlying pathophysiology.

Essentials to Remember

- Assessing a child's degree of respiratory impairment can be difficult during severe asthma exacerbations.
- Increased airway resistance, dynamic hyperinflation, and mucous production each contribute to alterations in pulmonary mechanics that can change widely and rapidly during a child's hospitalization.
- Although potentially lifesaving in children with acute asthma, intubation and mechanical ventilation are associated with significant complications and should not be undertaken lightly.
- Prior to intubation, a clinician must weigh the probability of improvement, the potential for respiratory arrest, and the potential complications.

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Vera Bernet

Educational Goals

- To review clinical presentation of diaphragmatic palsy and its pathophysiological mechanism leading to respiratory problems, especially in children of younger age
- To provide a treatment schedule for different age groups

52.1 Clinical Diagnosis and Severity Assessment

Diaphragmatic palsy or paralysis (DP) due to phrenic nerve injury is a rare respiratory condition which may be life-threatening in newborn and young children (Affatato et al. 1988; Haller et al. 1979; de Leeuw et al. 1999). This entity was first described in 1906 in an adult (Stauffer 1979). In newborn patients in the middle of the last century, it was most often due to birth trauma. In the days of advanced neonatal and cardiac surgery, DP is mostly a complication of thoracic surgery (Greene et al. 1975; Schwartz and Filler 1978; Stauffer and Rickham 1972; Stone et al. 1987; Zhao et al. 1985). The incidence is described

between 0.3 and 12.8 % and can be unilateral or bilateral (de Leeuw et al. 1999; Schwartz and Filler 1978; Kunovsky et al. 1993; van Onna et al. 1998). DP due to inflammation, neuropathic or idiopathic is rarely seen in this age group.

Clinical manifestation of DP depends on the unilateral or bilateral involvement and the presence of other respiratory problems. In newborn and infants DP most often presents with respiratory distress, presence of thoracoabdominal asynchrony, recurrent atelectasis, pneumonia, inability to wean from the ventilator or reintubation. Older children can compensate the loss of diaphragmatic function and usually present with little or no symptoms when only one side is affected (van Onna et al. 1998; Langer et al. 1988; Mickell et al. 1978; Serraf et al. 1990; Shoemaker et al. 1981; Tönz et al. 1996; Watanabe et al. 1987). Significant respiratory distress in adults is rarely seen if only one side is affected, because accessory muscles of respiration can compensate for the loss of diaphragmatic function. If both sides are affected, the patients present usually with severe exertional dyspnoea (Kumar et al. 2004). In children with single-ventricle physiology and Fontan circulation, DP is haemodynamically not well tolerated and may present with cardiac insufficiency, prolonged pleural effusion or ascites (Ovroutski et al. 2005).

With a better rib cage structural stability and ventilatory muscle strength, older children and adults can maximize ventilatory efficiency of a single functioning hemidiaphragm and minimize the paradoxical motion by passively tensing the

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paralyzed hemidiaphragm via its attachments to the expanding rib cage (Robotham 1979).

Infants, on the other hand, tolerate diaphragmatic paralysis less well than older children for different reasons. Infants are dependent on diaphragmatic contraction for adequate gas exchange, and if there is unilateral diaphragmatic paralysis, up to 50 % pulmonary function is lost. The intercostal muscles of infants are weaker, and there is a more horizontal orientation of the rib cage, so that DP cannot be compensated by a greater increase in intrathoracic dimension. Another reason is that infants have increased mediastinal mobility. This means that in the presence of DP, the mediastinal contents are shifted to the contralateral side on inspiration, while the paralyzed diaphragm is pulled upward. Pulmonary compliance is decreased on the ipsilateral side, so the diaphragm is unable to resist the negative intrapleural pressure and thus moves paradoxically with each respiration. This results in a significant reduction of the functional residual capacity of the affected and of the normal lung, alveolar collapse and formation of atelectasis. The usual recumbent position of infants and small children may lead to a greater reduction of vital capacity as in older children (Shoemaker et al. 1981; Tönz et al. 1996; Watanabe et al. 1987; Robotham 1979; Mok et al. 1991).

Several imaging modalities have been used to evaluate a diaphragm with suspected DP. The chest radiographs (X-ray) is not useful in its early diagnosis, especially in the neonatal period. Although most often DP is suspected by elevated hemidiaphragm on X-ray or computed tomography, this is not a specific sign because of the wide normal range of the position of the hemidiaphragm (Chetta et al. 2005). Confirmation requires diaphragm mobility tests like fluoroscopy or ultrasound. In the late 1990s ultrasound started to be the diagnostic tool of choice to diagnose DP. Multiple studies could show that ultrasound has advantages over fluoroscopy including portability, lack of ionizing radiation, visualization of structures of the thoracic bases and upper abdomen and the ability to quantify diaphragmatic motion (Alexander 1966; Houston et al. 1995; Gerscovich et al. 2001; Epelman

et al. 2005; Miller et al. 2006). In earlier years and still in some hospitals, fluoroscopy was the gold standard to secure diagnosis. Not much intention has been given to the use of magnetic resonance (MR) navigator echo monitoring of the diaphragm so far (Taylor et al. 1999). This might be due to the difficulty to move sick patients and especially children to the MR. Another modality available to confirm the diagnosis of diaphragm paralysis is phrenic nerve stimulation (PNS) and diaphragmatic electromyography (EMG). Both methods are frequently used in adults but difficult to use in infants and newborn. In PNS the nerve is electrically stimulated using percutaneous or needle electrodes or a single posterior cervical coil. EMG is either recorded from cutaneous electrodes between the seventh and ninth intercostal space in the anterior axillary line or from oesophageal electrodes. Mechanical response of the diaphragm is detected and measured by the elicited transdiaphragmatic pressure (Pdi) twitch against a closed airway or compound muscle action potentials. In patients with neuropathy there is usually a prolonged latency and absence or reduced twitch pressure (Luo et al. 2000; Strakowski et al. 2007).

Most important for every examinations is that the patient is under spontaneous breathing. Even ventilation on continuous positive pressure can mask a DP by moving the diaphragm in a lower position. Positioning, quality of movement and paradox movement of the diaphragm should be taken into account.

52.2 Management

Resolution of diaphragmatic paralysis depends on the severity of the phrenic nerve injury. Apart from complete denervation, stretching or blunt trauma of the phrenic nerve usually causes transient phrenic nerve paralysis. In many cases of traumatic injury, normal diaphragmatic function would gradually return over the next 6–12 months, but this would implicate a respiratory support during these times for newborn and small infants.

In children with bilateral paralysis, there is a consensus that one side needs to be plicated.

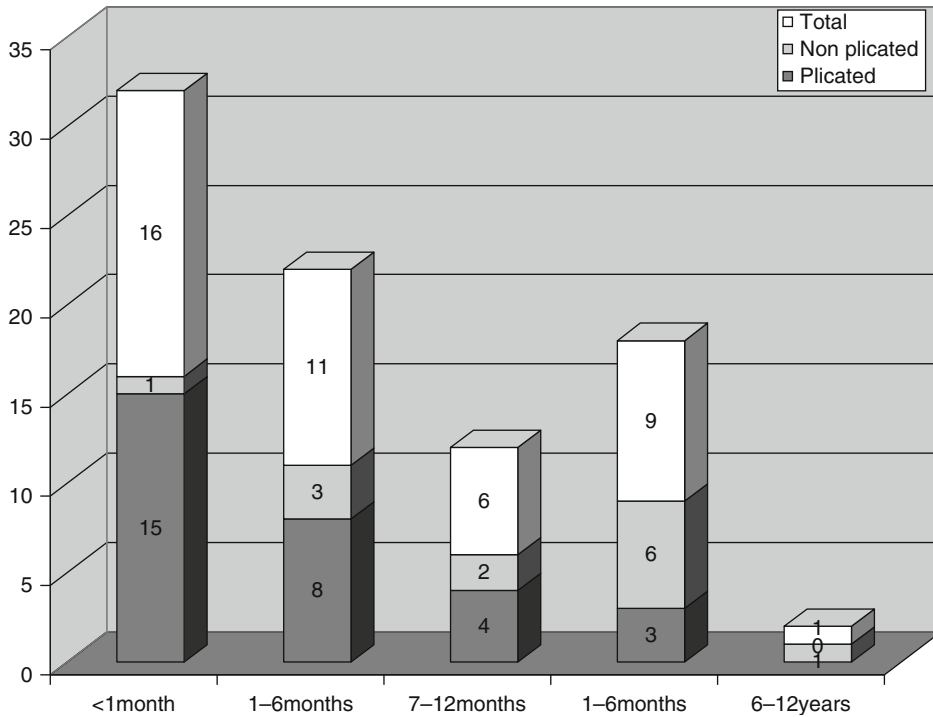


Fig. 52.1 Distribution of age in plicated and non-plicated patients (From Joho-Arreola et al. (2005) with permission)

However, some authors have reported recovery after 2–6 weeks after original operation (Haller et al. 1979; Langer et al. 1988; Mickell et al. 1978; Serraf et al. 1990; Hamilton et al. 1990). Time of intervention and treatment is discussed controversially and depends on the age of the patients.

In a study we published in 2005, we found an incidence of 5.4 % of infants with DP after cardiac surgery. In 42 infants we could show that children older than 6 months tolerated DP quite well, and it is reasonable to wait before plication is performed (Fig. 52.1) (Joho-Arreola et al. 2005). This can happen with noninvasive ventilation (NIV). In infants and older children, only PEEP is needed to reduce work of breathing until the diaphragm recovers (Bernet et al. 2005). This is most often applied either by a nasal or full face mask. Sometimes in small infants and newborns, NIV with patient-triggered positive pressure ventilation is needed to support the patients sufficiently (Robotham 1980).

In young infants under 6 months, plication should be performed after verification of the

diagnosis. We developed an algorithm for these patients (Fig. 52.2) (Joho-Arreola et al. 2005). In our institution, we used a thoracic approach as described by Bisgard (Cilley and Coran 1995). In all patients with unilateral paralysis, plication was performed through the seventh intercostal space with a lateral thoracotomy and fixation of the diaphragm on the ventral tenth costal arch. In three cases with bilateral pareses, only one side was plicated similarly with good result. Our results are comparable with the findings of Lemmer et al. which showed in a study of 74 children with congenital heart disease and DP after operation that mechanical ventilation, ICU stay and hospital stay are prolonged in newborns and young infants without plication (Lemmer et al. 2007). Baker et al. performed in 17 patients after DP plication fluoroscopy assessing diaphragm motion. Excursion of the plicated diaphragm was 77 % of the contralateral side. There was a trend toward improved function over time (Baker et al. 2008).

In a follow-up of 22 adult patients, Versteegh et al. could show that the patients after plication

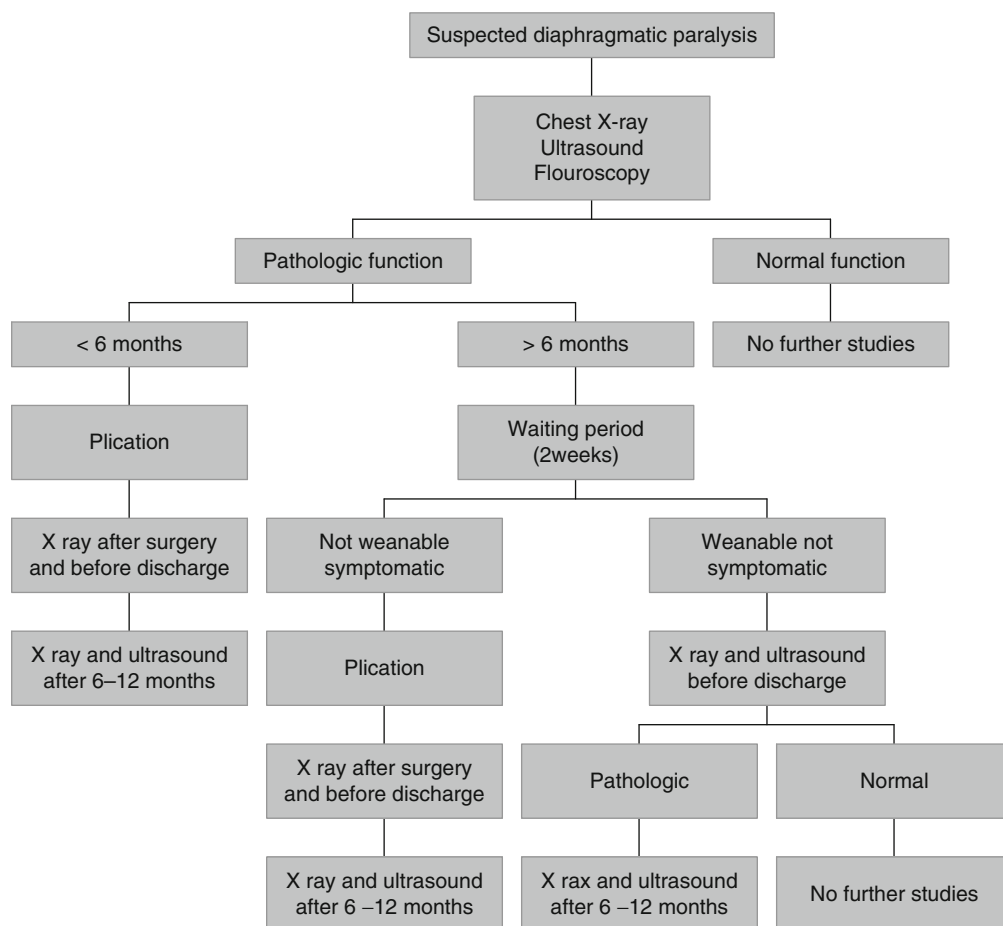


Fig. 52.2 Algorithm of patients with diaphragmatic paralysis (From Joho-Arreola et al. (2005) with permission)

improved in seated vital capacity, supine vital capacity and FEV₁. On the transient dyspnoea index, a remarkable improvement was noted in dyspnoea (Versteegh et al. 2007).

In children undergoing univentricular heart repair with non-pulsatile circulation like after Fontan operation, early diaphragm fixation seems to reduce morbidity like pleural effusions, ascites, duration of hospital stay and need for readmission (Talwar et al. 2010). Video-assisted thoracoscopic plication of the diaphragm has been described in a small case series in children and adults with good results (Freeman et al. 2006; Hines 2003). Hines described five patients between one week and 2 years who were successfully operated with a short ICU stay time (Hines 2003).

Diaphragmatic pacing has been used in adults and older children but not in infants. It requires an intact phrenic nerve and is not an option in bilateral paralysis. It is usually used in children with a nonsurgical origin of paralysis.

Essential to Remember

- Diaphragmatic paralysis is a typical complication after thoracic surgery and should be anticipated if babies cannot get off the ventilator.
- In children older than 6 months, a conservative treatment is eligible.
- Operative treatment is necessary in children under 6 months.

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Part XVIII

Cardiopulmonary Interactions in the Mechanically Ventilated Patient

Desmond Bohn

53.1 Introduction

The development in knowledge and understanding of cardiovascular and respiratory physiology has tended to proceed along parallel lines. However, many of the texts on cardiac physiology have tended to underestimate the major hemodynamic changes that occur during the transit of blood through the thoracic cavity from the venous to the arterial side of the circulation. Since the heart and lungs share the same body cavity, changes in pleural pressure associated with either spontaneous or mechanical ventilation have important effects on preload or afterload of both ventricles. With the development of intensive care and in particular positive pressure ventilation, we now have a greater appreciation that the heart and lungs are more than two independent but connected systems and events that occur in either organ will impact on the other. In critically ill children with severe acute hypoxic respiratory failure, high peak and positive end-expiratory pressure can have profound effects on both right heart filling and systemic output. In children with congenital heart disease, important cardiopulmonary interactions are best exemplified in obstructive right heart disease and palliated single ventricle with cavopulmonary shunts where changes in

intrapleural pressure have important effects on pulmonary blood flow. This chapter will begin with a discussion of the normal physiological changes associated with cardiopulmonary interactions before proceeding to deal with ventilation in pulmonary and cardiac disease (Table 53.1).

Table 53.1 Interaction between respiratory and cardiac function

The effect of changes in intrathoracic pressure on cardiac function

Spontaneous ventilation and normal heart

Positive intrathoracic pressure and systemic venous return

The effects of changes in intrathoracic pressure on pulmonary blood flow

The effect of changes in intrathoracic pressure on left heart function

The effects of positive end-expiratory pressure on cardiovascular function

Positive intrathoracic pressure in lung disease: the acute respiratory distress syndrome

The effect of changes in intrathoracic pressure in congenital heart disease

Intrathoracic pressure in tetralogy of Fallot and Fontan physiology

Positive pressure ventilation and the bidirectional cavopulmonary shunt

Positive pressure ventilation and ventricle lesions with duct-dependent systemic perfusion or systemic to pulmonary artery shunts

Positive pressure ventilation in left to right intracardiac shunts

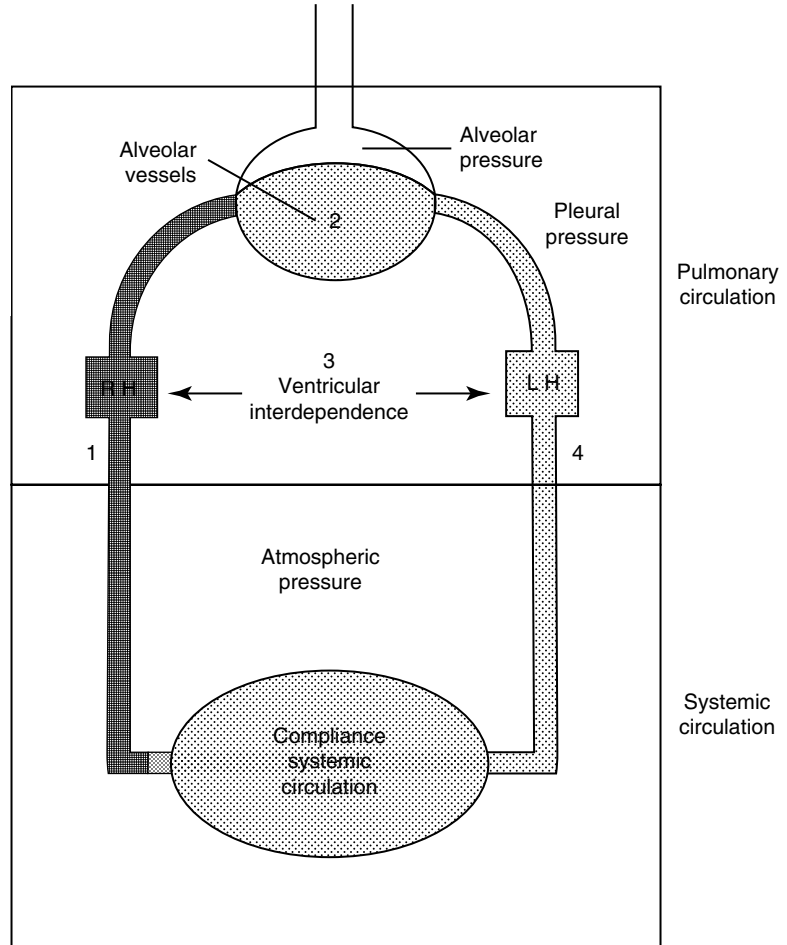
Cardiopulmonary interactions in acquired heart disease

Positive pressure ventilation and heart failure

The use of noninvasive continuous positive airway pressure in heart failure

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Fig. 53.1 A summary of cardiopulmonary interactions in a two-compartment model of the circulation. Both the right and left heart are subjected to pleural (intrathoracic) pressure, while the systemic vasculature is subjected to atmospheric or, in the case of the IVC, intra-abdominal pressure (From Permutt (1989))



53.2 The Effect of Changes in Intrathoracic Pressure on Cardiac Function

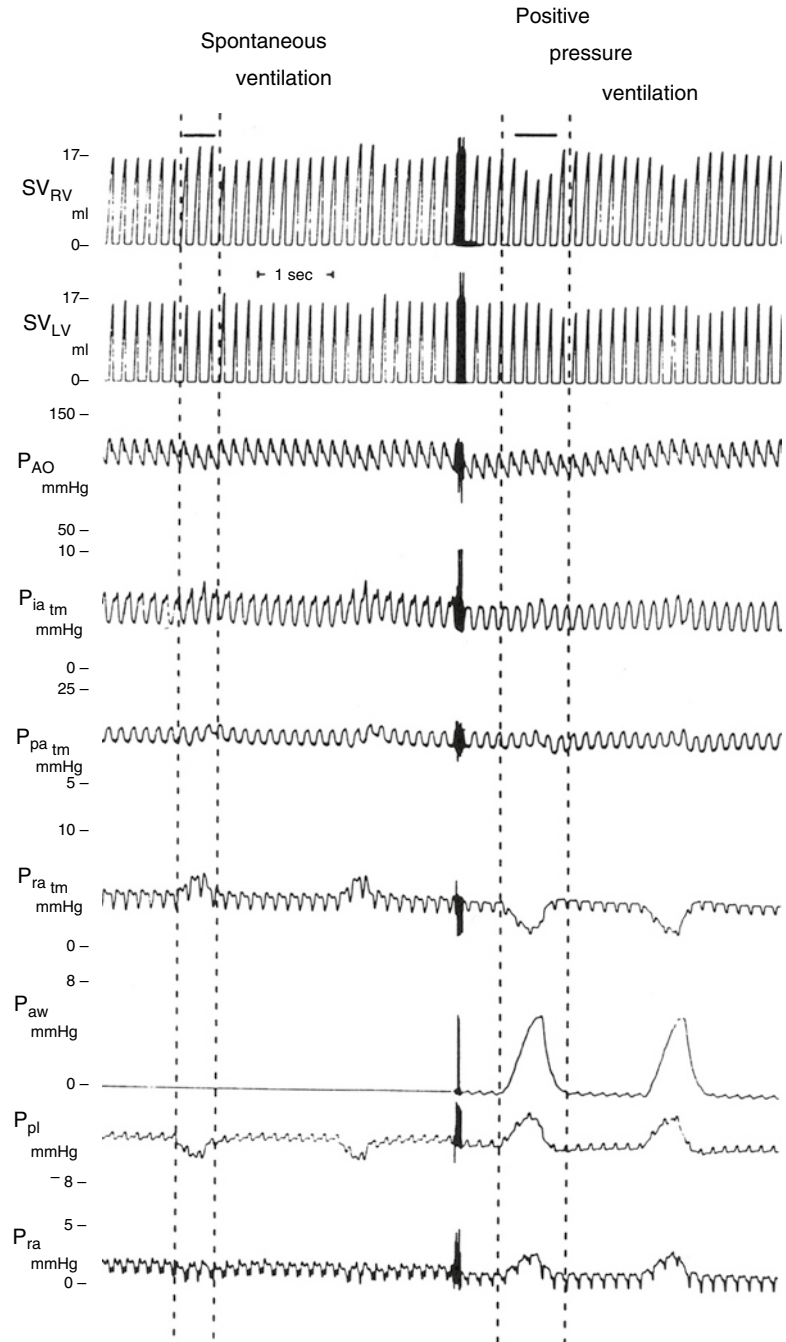
53.2.1 Spontaneous Ventilation and Normal Heart

Perhaps the easiest way to begin to understand the fundamentals of the complex interaction between the systemic and pulmonary circulations within the thorax is to use a model of two pumps connected in series enclosed within a chamber where the pressure is constantly changing. The reservoir for the filling of the right heart lies partly outside the thorax and is consequently subject to atmospheric or intra-abdominal pressure (IVC), whereas some of the large venous connections (SVC) are intrathoracic and subject to pleural pressure (Fig. 53.1). On the other hand,

the reservoir for left heart filling (the pulmonary circulation) and the systemic pumping chamber lie entirely within the thorax, although the pump ejects against a high impedance which is largely extrathoracic (systemic vascular resistance). Since pleural pressure is constantly changing during the respiratory cycle, it follows that the resulting fluctuations in intrathoracic pressure will affect the output from the pump by altering preload or filling on the right side and afterload or ejection on the left side.

The forces that govern venous return and how these are influenced by spontaneous respiration have been defined in the classic experiments of Guyton et al. (1954, 1955, 1957, 1958). The pressure generated for return of blood flow to the heart is the driving pressure (mean systemic pressure) minus the downstream pressure opposing venous return which in this instance is the right

Fig. 53.2 Changes in hemodynamics associated with spontaneous and positive pressure ventilation in the normal human. The area between the *dashed lines* represents the inspiratory phase. The reduction in pleural pressure during spontaneous inspiration increases right atrial filling and the right atrial pressure rises together with right ventricular stroke volume. There is a simultaneous fall in left ventricular stroke volume. During positive pressure ventilation right heart filling decreases, while LV stroke volume rises. For a more detailed explanation see text (From Pinsky (1991))



atrial pressure (P_{ra}). Acute elevations in right atrial pressure will result in a fall in cardiac output until compensated for by a change in compliance in the venous capacitance system. The pressure within the venous system is determined by the compliance and the volume of blood in the vascular bed and, with total circulatory arrest, the

mean systemic pressure is 7 mmHg on both sides of the heart (Guyton et al. 1955). The negative pleural pressure that occurs during a normal spontaneous inspiration produces a fall in right atrial pressure and hence the upstream pressure the venous capacitance sees, resulting in increased atrial filling (Fig. 53.2). The filling

pressure gradient for venous return to the right atrium is usually around 5 mmHg and is determined by the difference between the extrathoracic and intrathoracic venous pressures. As negative intrathoracic pressure increases the caliber of intrathoracic veins, one might suppose that a dramatic increase in venous return might occur during a reduction in right atrial pressure produced by a deep inspiration. In the normal human, there is flow limitation as this augmentation of venous return by negative intrathoracic pressure is limited by the fact that when pleural pressure becomes subatmospheric, the extrathoracic veins collapse at the thoracic inlet, limiting flow, while the intrathoracic cavae are maintained patent by a series of valves.

The interaction between respiratory and cardiac function is a complex one with major differences occurring under conditions of spontaneous or positive pressure respiration. These are illustrated in Fig. 53.2 which shows hemodynamic pressure changes during ventilation. The dashed lines represent the inspiratory phase of the respiratory cycle. During spontaneous breathing pleural pressure becomes negative during inspiration increasing the pressure gradient for venous return, transmural right atrial pressure ($P_{ra_{tm}}$) rises and right ventricular stroke volume (SV_{RV}) increases. Coincident with this there is a transient fall in left ventricular stroke volume (SV_{LV}) which is then augmented within a couple of cardiac cycles. The reasons suggested for this include the pooling of blood in the pulmonary circulation due to lung expansion, right heart filling causing a change in left ventricular diastolic compliance, or increased afterload on the left ventricle due to negative intrathoracic pressure. Positive inspiratory pressure on the other hand leads to a fall in $P_{ra_{tm}}$ as the rise in intrathoracic pressure decreases the gradient for venous return, filling of the atrium is impeded, and SV_{RV} falls, but there is a phase lag before this reduction is seen in the left heart. As intrathoracic pressure increases there is a very transient rise in SV_{LV} due to either reduced afterload on the LV or enhanced flow from pulmonary capillaries to the LA associated with the increase in intrathoracic pressure. This is more than offset by the

subsequent fall in SV_{LV} as right-sided events become predominant.

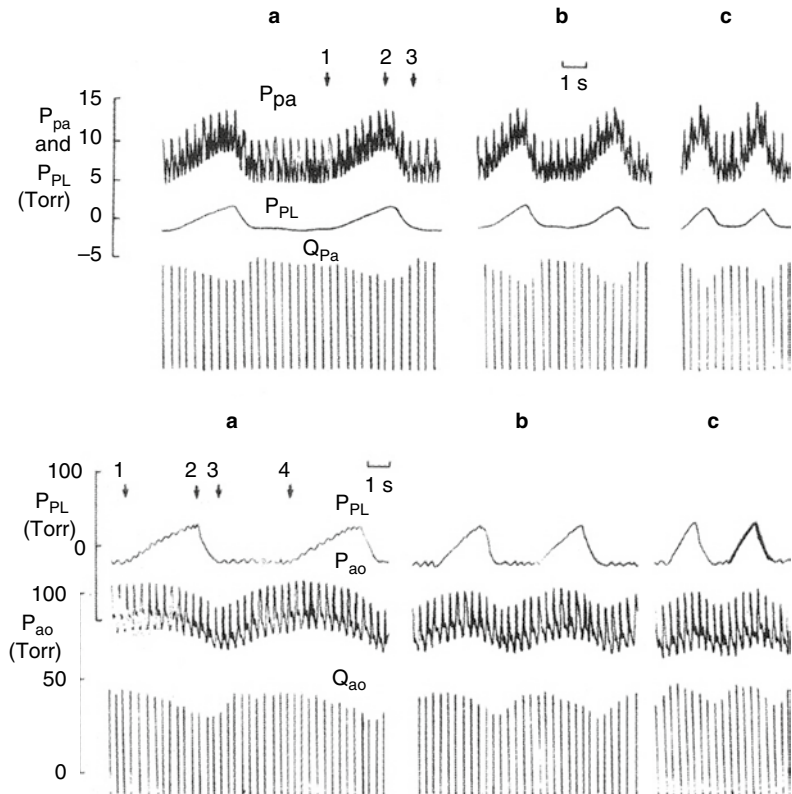
Two further factors influence the performance of the left and right ventricles; because there are cardiac muscle fibers that interconnect both ventricles and they share a common septum, changes in the contractile state of one ventricle will be reflected in the other, a phenomenon known as ventricular interdependence (Bove and Santamore 1981; Jardin 2003; Lloyd 1982). Both pumping chambers are also constrained within a viscoelastic membrane (the pericardium) which, while it does not normally have a significant influence on function, may inhibit contraction in situations where intrapericardial pressure increases. The interaction between respiratory and cardiac function is a complex one with major differences occurring under conditions of spontaneous or positive pressure respiration. Finally changes in lung volume, independent of any change in intrathoracic pressure, alter the caliber of the pulmonary vascular bed and thereby influence right ventricular afterload.

During ventilation gas moves in and out of the lung under the influence of changes in intrathoracic pressure (ITP). This results in important changes in hemodynamics which differ according to whether the change in ITP is negative or positive during inspiration or alveolar pressure is zero or positive at end expiration (PEEP). These changes are also influenced by underlying cardiac or respiratory disease. Although the term ITP is used generically to cover all pressure changes within the mediastinum, sometimes a differentiation needs to be made between it, pleural, alveolar, and transpulmonary (alveolar minus pleural) pressure.

53.2.2 Positive Intrathoracic Pressure and Systemic Venous Return

With the introduction of positive pressure ventilation, it was recognized from the outset that there were important effects on hemodynamics which were entirely different from spontaneous respiration. Cournand et al. (1948) was the first to show the association between the decreased

Fig. 53.3 Pulmonary and aortic blood flow during increasing rates of positive pressure ventilation (**a–c**) measured at 1) beginning of inspiration, 2) end inspiration, 3) end expiration, and 4) beginning of next inspiration. Aortic flow (Q_{ao}) begins to decrease shortly after the start of each inspiration reaching a nadir at end expiration. Aortic pressure (P_{ao}) on the other hand rises slightly to a peak which occurs closer to end inspiration at more rapid respiratory rates and reaches a nadir which is almost simultaneous with the nadir in Q_{ao} (From Scharf et al. (1980))



cardiac output and increased airway pressure in normal humans with mask positive pressure ventilation (PPV) experiments over 50 years ago. The explanation for this finding was that increased intrathoracic pressure is transmitted to the systemic venous system which resulted in reduced caval blood flow. The rise in right atrial pressure reduced the gradient for right atrial filling, which in turn leads to fall in right ventricular stroke volume (Fig. 53.2). The finding has been confirmed in numerous studies since then which have shown that in the absence of cardiopulmonary disease, positive intrathoracic pressure will reduce cardiac output through the mechanism of decreased venous return (Brecher and Hubay 1955; Charlier et al. 1974; Pinsky et al. 1985; Scharf et al. 1977, 1980) especially in situations of absolute or relative hypovolemia, while in the hypervolemic state pulmonary venous return to the LV would be increased due to augmented antegrade flow. The most graphic demonstration of this effect is when the increase in pleural pres-

sure occurs without a change in lung volume as in a Valsalva maneuver (Brooker et al. 1974; Korner et al. 1976; Parisi et al. 1976).

What has been less widely appreciated is that in the normal situation there is an initial increase in both aortic pressure and left ventricular output early in the inspiratory phase of positive pressure ventilation before falling towards the end of inspiration (Scharf et al. 1980; Jardin 2004; Morgan et al. 1966, 1969) and that this increase in aortic pressure is more pronounced at faster respiratory rates (Fig. 53.3). In contrast, changes in respiratory rate have little effect on pulmonary artery flow, which declines during inspiration and rises during expiration. It therefore appears that increased pleural pressure will have different effects on the right and left heart output at different phases of the respiratory cycle where a fall in pulmonary artery flow and rise in pulmonary artery pressure are seen at the same time as there is a rise in both pressure and flow in the aorta early in the inspiratory phase of positive pressure

ventilation. These differing effects require more detailed analysis. Among the theories that have been advanced to account for these differences are a phase lag due to pulmonary blood transit time, reduction in left ventricular afterload associated with positive pleural pressure, increased left ventricular preload due to forward flow of pulmonary venous blood due to lung expansion, and increased left ventricular compliance due to ventricular interdependence. The fact that pulmonary transit time has little or no bearing on the asynchrony between the right and left heart has been demonstrated in the intact animal by Robotham et al. (1983). In these experiments right heart output replaced by a roller pump to maintain a constant left-sided preload, aortic flow still increased during the early phase of inspiration despite the elimination of the variation in right ventricular output. In a further series of experiments in open-chest animals, where pleural pressure is no longer a factor and with the right heart decompressed eliminating the ventricular interdependence factor, Robotham has also been able to show that the application of positive pressure to the lung still resulted in increased left ventricular output (Robotham and Mintzner 1979).

Many of the studies of the effect of positive pressure ventilation on the right heart have been done in steady-state conditions after increases in ITP rather than examining the instantaneous effects of increases in airway pressure (Pinsky 1984). Also, many of these studies did not take into account the potential impact of the changes in intravascular volume status that might occur in patients might have on the relationship between ITP and venous return. Important information on caval blood flow is now available using echocardiography and pulsed Doppler techniques. Studies on changes in ITP in normal animals who are not hypovolemic have shown that mean systemic pressure is maintained even as ITP increases (Fessler et al. 1988). The explanation for this is as the diaphragm descends during inspiration, the increase in intra-abdominal pressure results in increased venous return by enhancing the splanchnic IVC flow (Takata and Robotham 1992; Takata et al. 1990). Under relatively hypervolemic conditions. P_{ra} exceeds

intra-abdominal pressure (P_{ab}), analogous to zone III conditions described for pulmonary blood flow in the lung (West et al. 1964). In situations of hypovolemia, however, P_{ab} exceeds P_{ra} (zone II) and the total IVC venous return is reduced (Takata and Robotham 1992; Kitano et al. 1999). These findings have been confirmed in humans. Van den Berg et al. (2002) has shown that in fluid-resuscitated postoperative cardiac surgical patients, increases of airway pressure up to 20 cmH₂O resulted in no change in cardiac output or RV end-diastolic volume. This was ascribed to the fact that there were parallel increases in P_{ra} as well as P_{ab} and therefore there was no effect on venous return. This study demonstrates that venous return can be maintained when ITP and P_{ra} increase as long as mean systemic pressure increases by an equivalent amount. This happens because the rise in P_{ab} compresses the liver and squeezes the lungs. The same does not apply if the patient is hypovolemic when increased ITP results in zone 2 conditions and collapse of the thoracic portion of the vena cava. A summary of these studies would conclude that venous return and stroke volume of the right heart increase due to the negative intrathoracic pressure associated spontaneous breathing, while positive ITP only significantly impacts on right heart filling when patients are hypovolemic or the level mean airway pressure is so high as to render them relatively hypovolemic. This will be discussed further in the section on ARDS. Paradoxically, in situations where severe right ventricular failure results in profoundly low cardiac output, ventilation with high peak inflation pressures at rapid rates may result in a rapid improvement in hemodynamics. Serra et al. (1988) have reported a dramatic improvement in four children with profound right ventricular failure after corrective cardiac surgery when switching from conventional ventilator settings to higher-frequency (50/min) high-volume (TV 30 ml/kg) ventilation. The increased MAP in this situation probably acts as a right ventricular assist device in increasing forward flow from a dilated and noncontractile right ventricle in much the same way that it produces forward flow in simultaneous ventilation-compression CPR.

Important new insights into the effect of positive intrathoracic pressure on right heart function in critically ill patients have been gained from the use of echocardiography and pulsed Doppler. These show that when tidal volume is progressively increased, the RV has to generate an increasingly higher pressure to open the pulmonary valve (Jardin et al. 1989). Increases in transpulmonary pressure (airway pressure minus pleural pressure) and tidal volume during the inspiratory phase of positive pressure ventilation result in a sharp but transient reduction in flow acceleration in the pulmonary artery. However, when airway pressure was increased without a change in tidal volume, there was no effect on RV afterload.

53.2.3 The Effects of Changes in Intrathoracic Pressure on Pulmonary Blood Flow

Ventilation influences PVR in a number of different ways. Changes in airway pressure (P_{aw}) transmitted to the alveoli during spontaneous and positive pressure ventilation alter pulmonary blood flow by changes in the caliber of pulmonary capillaries. Lung distention per se has significant neurohormonal effects on PVR and right ventricular function via the vagus nerve and the release of prostanoids, ADH, atrial natriuretic peptide, and catecholamines (Berry et al. 1971; Edmonds et al. 1969; Farge et al. 1995; Frass et al. 1993; Glick et al. 1969; Payen et al. 1987). There is also the important effect of pH on PVR mediated by altering P_{aCO_2} , independent of any change in lung volume.

For the purposes of examining the effect of the change in P_{aw} on pulmonary vascular resistance, it has been convenient to think of pulmonary vessels as being divided into two functional groups; the large pulmonary vessels and the heart which sense changes in interstitial pressure in the lung and those which are exposed to an extravascular pressure which reflects alveolar pressure (intra-alveolar vessels). The change in blood flow in the intra-alveolar vessels depends on their position within the different zones of the lung as outlined by Permutt and West (West et al. 1964;

Permutt et al. 1962) who defined the relationship between pressures in the alveolus (PA) and pulmonary artery (Pa) and left atrium (Pla). Where zone I (lung apex) conditions apply, the pressure within the arterial end of the vessel is less than alveolar pressure ($PA > Pa > Pla$) and is therefore insufficient to open the vessels, which remain collapsed and there is no flow (Hughes et al. 1968). These conditions exist in the uppermost parts of the lung in the upright human or in the superior part of the lung when lying supine. Where zone II conditions apply ($Pa > PA > Pla$), arterial pressure is higher than alveolar and the intra-alveolar vessels behave like Starling resistors surrounded by alveolar pressure where flow depends on the difference between arterial and alveolar pressures and is independent of changes in left atrial pressure. These conditions predominate in the mid zone of the lung in the upright and supine human and can also be seen during the inspiratory phase of positive pressure ventilation (Jardin and Vieillard-Baron 2003). In zone II conditions, the back pressure to right ventricular ejection is alveolar rather than left atrial pressure, and the relevant resistance is only that between the pulmonary artery and the downstream end of the alveolar vessels. An increase in lung volume produces an increase in back pressure to right ventricular ejection compared with the pressure around the heart and increased afterload. This requires that an approximately equal increase in pressure be produced in the pulmonary artery and alveolus to maintain pulmonary blood flow, which translates into increased right ventricular wall stress. Thus, an increase in alveolar relative to pleural pressure increases right ventricular afterload, and it is this change in alveolar pressure relative to arterial that can produce a marked degree of increased afterload seen in acute asthma (Permutt 1973). In zone III conditions ($Pa > Pla > PA$), the pressure in the venous side of the capillary is higher than alveolar pressure, and pulmonary blood flow behaves like a Starling resistor where flow is independent of alveolar pressure and is governed by the difference between pulmonary arterial and venous pressures. These conditions predominate in the dependent lung regions.

The effect of a change in lung volume on extra-alveolar vessels is somewhat different. An increase in lung volume during inspiration increases radial traction on extra-alveolar vessels, increasing their caliber and causing a fall in pulmonary vascular resistance and a decrease in right ventricular afterload. The net effect of these various changes is that pulmonary vascular resistance is lowest at FRC and is minimally changed at airway pressures of 5–10 cmH₂O and rises in situations where vessels are compressed during lung collapse or where there is overdistention of the lung. Loss of FRC, as seen with the development of pulmonary edema or atelectasis, will result in a rise in pulmonary vascular resistance, as will overdistention of the lung due to airway obstruction or high peak airway pressure ventilation that puts the lung on the flat portion of the pressure-volume curve. In this situation zone I conditions would predominate throughout the lung ($P_A > P_a > P_{la}$) and pulmonary vascular resistance would be increased.

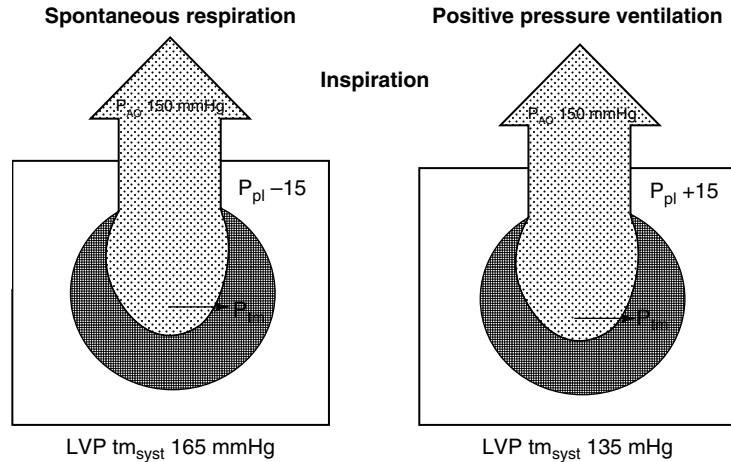
53.2.4 The Effect of Changes in Intrathoracic Pressure on Left Heart Function

The changes in intrathoracic pressure produced by respiration have important and hitherto underappreciated effects on left ventricular function which assume greater importance in the failing heart. In order to evaluate the significance of these various forces and the effect of positive or negative intrathoracic pressure on left ventricular preload and afterload, it is important to understand the changes in cardiac output and left heart function secondary to respiration.

The most commonly observed change in left heart function that occurs with spontaneous respiration is an initial fall in arterial pressure during inspiration due to a decrease in left ventricular stroke volume (Fig. 53.2). The reasons for this have been largely attributed to events occurring on the right side of the circulation and include (1) the pooling of blood in the pulmonary circulation due to lung expansion, (2) a phase lag between right and left ventricular output, (3) the stimula-

tion of systemic baroreceptors or pulmonary stretch receptors, and (4) impeded right heart filling causing a change in left ventricular diastolic compliance or ejection mediated through ventricular interdependence. Although studies of pulmonary transit time have shown that it takes one to two cardiac cycles for a change in right-sided output to be reflected in the left side (Franklin et al. 1962; Maloney et al. 1968), the phase lag theory is unlikely to fully explain the decrease in left ventricular ejection associated with a reduction in intrathoracic pressure. Changes in right heart output must also affect the left side as the two circulations are connected in series, which accounts for the observation that blood pressure and left ventricular stroke volume may rise after an initial fall. In this situation, the increase in venous return eventually overrides the other factors that tend to impede left ventricular output. Neural receptors that have been suggested to influence left ventricular function include stretch receptors in the lung mediated via the vagus nerve and intra- and extrathoracic baroreceptors that are mediated by the autonomic system. There is reliable experimental data to suggest that neither of these is likely to be a major mechanism in the fall of left-sided output. Robotham et al. (1979) found that there were still significant falls in left ventricular stroke volume in vagotomized animals during a Mueller maneuver (inspiratory effort against a closed glottis), where intrapleural pressure falls but lung volume remains unchanged. A decrease in left ventricular stroke volume during inspiration is still seen even after autonomic blockade of vagal and sympathetic efferent nerves. If left atrial and ventricular diastolic pressures were measured relative to atmosphere, then one could demonstrate a fall in these pressures during inspiration, which would support the concept that the principal cause of the decrease in left-sided output during inspiration was pooling of blood in the lungs secondary to lung expansion. However, it has been shown that during inspiration in both the intact animal and the isolated lung preparation, pulmonary venous return actually increases at the same time that left ventricular stroke volume is falling (Guntheroth et al. 1967; Howell et al. 1961). This apparent

Fig. 53.4 Changes in afterload on the left ventricle associated with the inspiratory and expiratory phase of spontaneous ventilation. The numbers for pleural and intracavity pressure are arbitrary and chosen only to illustrate the point that afterload (end-systolic pressure) increases during inspiration. $LVP\ t_{m_{syst}}$ left ventricular transmural systolic pressure



paradox is explained when these pressures are related to intrapleural pressure where it can be shown that transmural (intracavity minus intrapleural) filling pressures on the left side actually increase during inspiration. Thus it is more valid to define the afterload as being the left ventricular transmural pressure which in this instance is the intracavity pressure minus the intrapleural pressure (Fig. 53.4).

The observation that afterload increases with negative intrathoracic pressure has been confirmed by studies of left ventricular function during spontaneous breathing with increased inspiratory loads which demonstrated that both left ventricular end-diastolic and end-systolic volumes are increased (Scharf et al. 1979a, b). However this occurs independently of changes in lung volume as has been demonstrated in experiments which showed that afterload was found to increase during a Mueller maneuver. Both Brinker et al. (1980) and Guzman et al. (1981) have also confirmed septal wall displacement during the Mueller maneuver which was associated with decreased diastolic compliance and volume of the left ventricle. Sustained decreases in intrathoracic pressure have also been shown clinically to result in mild degrees of left ventricular dysfunction when associated with ischemic heart disease (Scharf et al. 1981).

Various mechanisms have been invoked to explain the marked fall in left ventricular stroke volume arterial blood pressure that occurs with

large negative intrathoracic pressures during spontaneous respiration during severe airway obstruction. It has been difficult to determine whether this is due to decreased left ventricular filling or increased afterload because left ventricular filling and emptying may occur simultaneously with inspiration extending over several cardiac cycles. In a series of experiments, Peters et al. (1988a, b) has attempted to clarify this issue by synchronizing negative intrathoracic pressure with systole and diastole independently. The findings would suggest that negative intrathoracic pressure with the airway obstructed during systole reduces left ventricular stroke volume predominantly by increasing afterload and impedance to blood flow out of the thorax. When negative intrathoracic pressure was synchronized with diastole, left ventricular output fell due to ventricular interdependence.

Since the generation of large negative intrathoracic pressures can impede both diastolic and systolic performance of the left ventricle, it is not surprising that this will occasionally result in acute left ventricular failure and the development of pulmonary edema. This has been well documented during acute upper airway obstruction occurring with laryngospasm during anesthesia (Cozanitis et al. 1982; Jackson et al. 1980; Lee and Downes 1983) and with croup and epiglottitis (Oswalt et al. 1977; Stradling and Bolton 1982; Travis et al. 1977). It may also occur following the relief of upper airway obstruction (Sofer et al.

1984) and during status asthmaticus where at the peak of inspiration negative intrathoracic pressures of up to minus 40 cmH₂O can be produced (Stalcup and Mellins 1977). The overall effect of a negative intrathoracic pressure on left ventricular function is therefore a balance between its effect on the preload and left ventricular systolic ejection (afterload). The increase in afterload due to negative pleural pressure is one of the mechanisms responsible for the worsening of heart failure seen with obstructive sleep apnea (Naughton et al. 1994, 1995a). It may become even more pronounced in situations of decreased lung compliance such as pulmonary edema or lung disease where there are increasingly negative swings in intrathoracic pressure (Naughton et al. 1995b).

The effect of positive pressure ventilation on the left heart is particularly relevant in critical care medicine. The following considerations need to be taken into account: (a) right heart preload and septal shift influence LV end-diastolic volume; (b) there is a phase lag before this is manifest in left heart output; (c) the effect is most pronounced at end inspiration; (d) there is a difference between increased pleural pressure, which impedes venous return, and increased lung volume, which both compresses the heart and increases the pulmonary extra-alveolar capacity; and (e) at peak inspiration ITP affects systolic performance and this is significantly influenced by the underlying function of the LV. Attempts have been made to separate these different effects by examining ventricular function during apnea, by synchronizing ventilation with ventricular systole using a jet ventilator, by changing alveolar pressure independent of ITP with an abdominal binder, and by examining the effect of PPV in a heart failure model induced by beta blockade.

Positive pressure ventilation alters left ventricular function by both mechanical forces and changes in lung volume. An increase in ITP alters diastolic compliance and pericardial pressure. The net result is a decrease in left ventricular end-diastolic volume due to decreased preload but no change in systolic right ventricular function. Several studies have shown that left ventricular dimensions are altered by both intermittent positive pressure ventilation and PEEP in that the septal to free wall and

anterior to posterior minor axis dimensions diminish, which is consistent with an overall decrease in left ventricular end-diastolic volume (Robotham et al. 1979, 1985; Visner et al. 1983). The effect is greater in the septal to free wall dimension, which suggests that ventricular interdependence is the important mechanism that contributes to the decreased left ventricular preload seen with the application of PEEP.

Positive pressure ventilation-induced changes in lung volume also affect left ventricular function independent of the change in intrathoracic pressure. Lung expansion changes the capacitance of the pulmonary venous system thereby altering pulmonary blood flow depending on the underlying pulmonary blood volume and vascular tone (Brower et al. 1985). Increasing lung volume will also restrict cardiac filling in a similar fashion to cardiac tamponade by encroachment of the lung on the cardiac fossa (Lloyd 1982). This may have important implications in positive pressure ventilation in status asthmaticus where overinflation of the lung caused by rapid respiratory rates and inadequate expiratory time can result in low output and cardiac arrest. A dramatic illustration of this is provided in a case report of an adult with severe asthma who had a cardiac arrest after intubation and had all the features of cardiac tamponade (Rosengarten et al. 1991). The usual resuscitation techniques failed including prolonged expiratory time ventilation. After CPR was abandoned spontaneous circulation resumed after 3 min of apnea. This demonstrates how severe gas trapping can have a profound on cardiac function.

Recently more sophisticated techniques for measuring left heart performance using cardiac echo and conductance catheters have become available. These have allowed investigators to measure chamber size and display pressure-volume loops of the LV while lung volume and ITP were altered (Denault et al. 2001). These studies have shown that the influence of ventilation on LV function is complex and influenced by pulmonary mechanics, circulating volume status, and the underlying contractile state of the ventricle. When ventricular function is normal and there is a normal circulating volume, the preload

effect predominates, and increase in ITP at end inspiration results in a decrease in LV end-diastolic volume, without a change in systolic performance. As this occurs at the same time as there is a rise in LV end-diastolic pressure, the purported mechanism is compression of the heart by the lungs. When contractility is impaired and ventricular volumes are increased, positive pressure inspiration reduces LV end-systolic volume by lowering afterload and improving ejection (Denault et al. 2001). This has important implications for the treatment of heart failure, as will be discussed later.

53.2.5 The Effects of Positive End-Expiratory Pressure on Cardiovascular Function

The effects of PEEP on cardiovascular function have been a source of major interest in critical care medicine since the original description of its use in ARDS over 30 years ago. These include the potential for diminished myocardial contractility and ventricular compression by lung distention (Lloyd 1982) as well as the overall effect on cardiac output. However, it is frequently difficult to separate the effect of PEEP independent of the peak airway pressure as a change in both results in a change in the mean airway pressure (MAP). The application of PEEP in the normal human and animal heart results in a fall in cardiac output due to decreased preload (venous return) and increased afterload (pulmonary vascular resistance) (Rankin et al. 1982). In addition, Doppler flow studies have shown backward flow of blood through the tricuspid valve (Jullien et al. 1995). PEEP, in addition to increasing pleural pressure, will increase lung volume and FRC depending on lung and chest wall compliance. If it overdistends the lung and increases pulmonary vascular resistance, an increase in right ventricular volume will occur which may adversely affect left ventricular compliance by leftward shift of the intraventricular septum. However, in the situation where the appropriate amount of PEEP is being used, lung volume will be recruited and the end-expiratory volume will be at functional residual capacity

(FRC) and pulmonary vascular resistance will fall. High levels of PEEP have been shown to compromise flow in a marginal right coronary circulation because of decrease in flow associated with the rise in right ventricular systolic pressure and intrapericardial pressure (Fessler et al. 1988; Bishop et al. 1976; Brooks et al. 1971). Similar observations on the differing effect of PEEP on right ventricular ejection fraction have been made on adults with ischemic heart disease after cardiopulmonary bypass (Boldt et al. 1988). Patients with pronounced right coronary artery stenosis had diminished right ventricular ejection fraction and increased right ventricular end-diastolic volume, whereas there was no effect in patients with minor coronary artery stenosis.

53.3 Positive Intrathoracic Pressure in Lung Disease: The Acute Respiratory Distress Syndrome

One of the most important areas where positive intrathoracic pressure potentially impacts on cardiovascular function is in patients with acute respiratory distress syndrome (ARDS). The current focus on lung recruitment strategies using high PEEP as part of the open lung approach, while improving oxygenation, pays scant attention to what impact this might have on cardiac function. If the only consideration were an improvement in oxygenation, then it would simply be a case of increasing PEEP until the best PaO_2 at the lowest FiO_2 was achieved. However, the potential adverse effects of PEEP on cardiovascular function mean that the most important therapeutic goal is the level of PEEP that gives the best combination of oxygenation and cardiac output, thereby achieving maximum oxygen delivery (oxygen content $\times$ cardiac output). Given that ARDS is a multisystem disease, it is important that we focus our attention on how positive pressure ventilation, PEEP, and lung disease affect the other major organ that shares the chest cavity.

In the past, attempts to define the effects of PEEP on the cardiovascular system have relied on studies in intact animals and small studies in

humans using intracardiac pressure measurements from pulmonary artery catheters in normal and disease states. These studies have shown that the magnitude of changes depends partly on factors that influence the underlying cardiovascular status (circulating volume, ventricular dysfunction, increased pulmonary vascular resistance) and on factors within the lung that may modulate the transmission of airway (alveolar) pressure to the pleural space and consequently to the heart and vascular structures. Decreased lung compliance will reduce pressure transmission while increased thoracic compliance will enhance it (Jardin et al. 1985a; Pontoppidan et al. 1977). Taking all these factors into consideration, it is not unusual to see a fall in cardiac output and stroke volume with high levels of positive pressure ventilation with PEEP in ARDS. The mechanisms that have been invoked as a cause for this decrease include decreased venous return, increased right ventricular afterload, decreased left ventricular compliance, and decreased ventricular contractility. However, these studies are limited by the fact that pressure was measured rather than changes in volume.

The importance of right ventricular function in patients with ARDS has been the subject of increasing attention (Jardin et al. 1985b, c, 1989; Jardin and Vieillard-Baron 2003; Hurford and Zapol 1988; Jardin and Bourdarias 1997; Vieillard-Baron and Jardin 2003; Vieillard-Baron et al. 2001a). As is seen with positive pressure ventilation in the normal lung, the increase in pleural pressure with PEEP will reduce venous return to the right heart in ARDS (Dhainaut et al. 1986; Potkin et al. 1987; Viquerat et al. 1983), and this is frequently compensated for by giving fluid to increase filling pressures. In patients with severe acute respiratory failure, levels of PEEP above 10 cmH₂O have also been associated with an increase in right ventricular afterload (Dhainaut et al. 1986; Viquerat et al. 1983; Calvin et al. 1981; Jardin et al. 1984). In the setting of severely depressed baseline right ventricular ejection in humans, the application of PEEP has been shown to result in the depression of contractile function (Schulman et al. 1988). Following right coronary artery ligation in animals, right ventricular ejection

fraction declined associated with an increase in end-systolic volume (Schulman et al. 1990). Even in the absence of overt ischemia, acute right heart dysfunction has been identified as a cause of morbidity and mortality in ARDS (Monchi et al. 1998). This is not only due to the effects of ventilation and PEEP but also as a result of the underlying lung disease. The alveolar collapse and microvascular obstruction cause an increase in PVR and pulmonary artery pressure (Zapol and Snider 1977). There is an association between this increase in PVR and mortality (Squara et al. 1998).

The more widespread use of echocardiography and pulsed Doppler has improved our understanding of the effect of PEEP on right heart function or cor pulmonale in ARDS. Before the advent of reduced tidal volume ventilation, a 61 % incidence of acute cor pulmonale, defined as paradoxical septal motion with acute RV enlargement, was reported in adults with ARDS (Fig. 53.5) (Jardin et al. 1985c). More recently the same investigators have reported a 25 % incidence in a study where tidal volume was limited to 8 ml/kg (Vieillard-Baron et al. 2001a). Another study compared the effect on pulmonary blood flow at zero PEEP with two other levels, one determined by the highest value of lung compliance and the second the coordinates for the lower inflection point on the lung pressure-volume curve (Schmitt et al. 2001). They found that the PEEP level that had the least effect on RV impedance was that associated with the highest compliance (6 ± 3 cmH₂O), a number remarkably similar to that found in the best PEEP study by Suter 35 years ago (8 cmH₂O) (Suter et al. 1975). In a landmark study in 1981, Jardin et al. (1981) measured right and left heart pressures together with measurements of chamber size with echo while PEEP levels of up to 25 cmH₂O were applied. He found that increasing levels of PEEP were associated with a gradual decrease in left ventricular end-systolic and end-diastolic dimensions as lung hyperinflation induced increased RV afterload as leftward shift of the septum encroached on the LV cavity (Fig. 53.6). The thin-walled RV dilates as afterload increases, but the free wall is constrained by the pericardium, and therefore it can only dilate leftwards as the end-diastolic

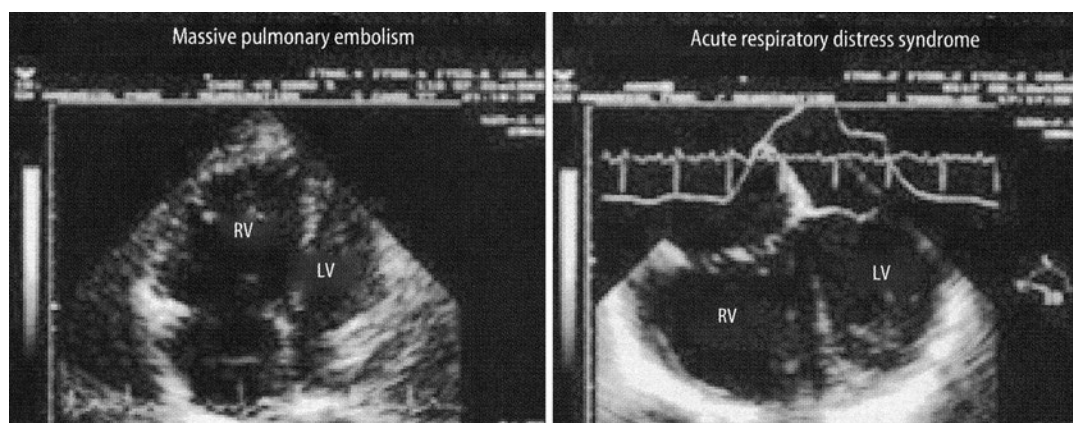
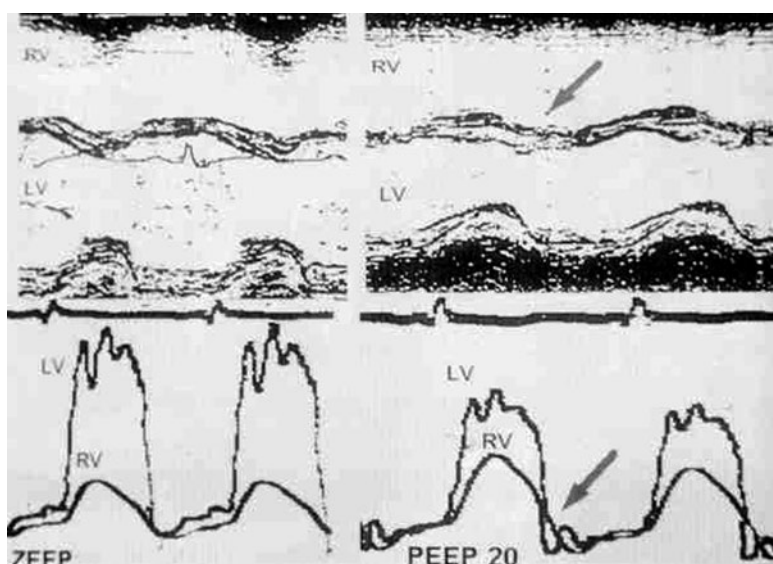


Fig. 53.5 Two examples of acute right heart dilatation affecting left heart compliance in acute pulmonary embolism and ARDS. The septum is shifted leftwards and encroaches on the LV Left ventricle cavity (From Jardin (2003))

Fig. 53.6 *Top:* cardiac M-mode echo recording of septal wall motion before and after the application of 20 cmH₂O PEEP. This produces paradoxical septal motion with leftward displacement at end systole (arrow). *Bottom:* simultaneous RV and LV pressure recordings which show reversal of the transseptal pressure gradient at end systole (arrow) and diastolic pressure equalization, maintaining the IVS in a shifted position (From Jardin et al. (1997))



volume increases. In previous studies the reduction in cardiac output was frequently compensated for by expansion of circulating volume, which increased right ventricular preload and right ventricular myocardial segment length (Dhainaut et al. 1986; Viquerat et al. 1983; Calvin et al. 1981; Jardin et al. 1981; Prewitt et al. 1981; Qvist et al. 1975). In these studies, however, the fall in cardiac output could be compensated for by infusing volume only in patients who were on low levels of PEEP. Left ventricular contractility was unaltered by any level of PEEP.

Echocardiography has been a very useful tool in helping us understand more ventilation-induced changes in intrathoracic pressure and intravascular volume in patients with sepsis and ARDS. Investigators have used echo, pulsed Doppler, and interrogation of the arterial pulse pressure to evaluate changes in chamber dimensions, collapsibility of the great veins, and the response to volume loading (Jardin 1997, 1999, 2003, 2004; Jardin and Bourdarias 1997; Vieillard-Baron and Jardin 2003; Jardin et al. 1997; Vieillard-Baron et al. 1998, 1999, 2001a,

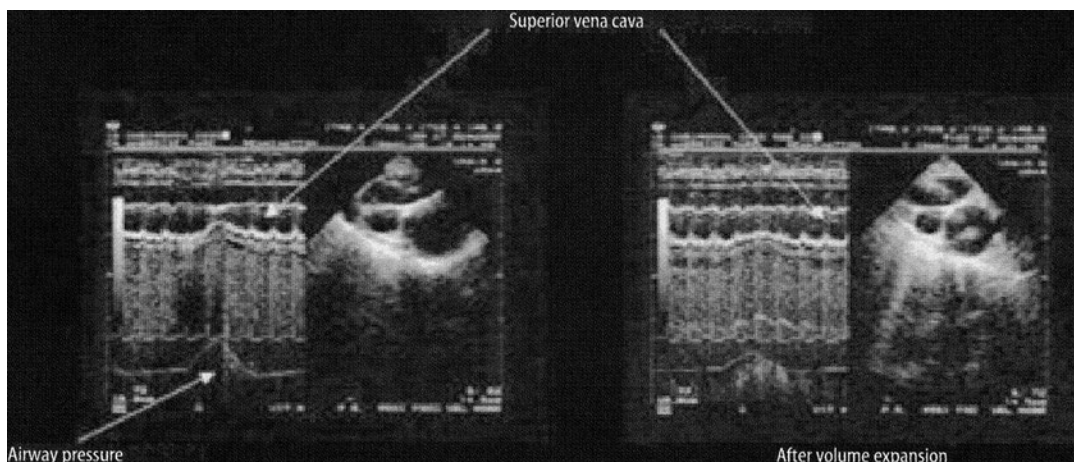


Fig. 53.7 Illustration of the effect of positive ITP on SVC flow in a patient before and after volume expansion. The SVC demonstrates “collapsibility” at peak inspiration prior to volume expansion (From Jardin (2003))

b, c, 2002a, b, 2003a, b, c, 2004). It has long been recognized that arterial pressure rises during positive pressure lung inflation, a phenomenon sometimes referred to as reversed pulsus paradoxus (Jardin et al. 1983; Massumi et al. 1973). The changes in pulse pressure can be described as a succession of inspiratory increases followed by expiratory decreases (Jardin 2004). Studies in humans with sepsis and respiratory failure have shown that at peak inflation the LV stroke volume increases while that of the RV falls. The increase in alveolar pressure is associated with an increase in LA size and an augmented Doppler flow signal in the pulmonary veins as the capillaries are squeezed (Vieillard-Baron et al. 2003a). At the same instant RV stroke volume falls because of an increase in impedance (Vieillard-Baron et al. 1999), while the delay in refilling of the capillary bed results in a drop in arterial pulse pressure back to the pre-inspiratory level as the filling reserve of the LV falls in the next few cardiac cycles (Vieillard-Baron et al. 2003a; Preisman et al. 1997). In patients who are hypovolemic, there is a pronounced fall in arterial pulse pressure reflecting predominantly a reduction in RV preload which results in reduced LV stroke volume. The amplitude of the expiratory decrease has been used to detect fluid responsiveness (Michard et al. 2000; Tavernier et al. 1998).

Vieillard-Baron and co-workers have also used echocardiography measurements of IVC and SVC size during inspiration and expiration to diagnose hypovolemia (Vieillard Baron et al. 2001; Barbier et al. 2004) and used a “collapsibility” index to help guide fluid administration in ventilated patients with sepsis (Vieillard-Baron et al. 2001b, c) (Fig. 53.7).

Similar principles that govern the increase ITP associated with PPV govern the use of non-invasive ventilation in ARDS. Depending on the underlying lung compliance, patients who are capable of maintaining adequate spontaneous ventilation in ARDS with use of CPAP may achieve better oxygenation for the same level of PEEP with less adverse hemodynamic effect and therefore better oxygen delivery due to the lower mean airway pressures (Schlobohm et al. 1981; Shah et al. 1977; Simonneau et al. 1982). Dhainaut et al. (1986) have observed that when patients were changed from spontaneous respiration to CPAP in ARDS, there is a decrease in right ventricular end-systolic and end-diastolic volumes, suggesting a fall in right ventricular afterload. Jardin et al. (1984) have observed the opposite effects in normal subjects without lung disease. The explanation for this discrepancy lies in when FRC is normal, pulmonary vascular resistance is at its lowest, and right ventricular

afterload is minimal. The application of CPAP in normal individuals will increase lung volume above FRC and compress the extra-alveolar vessels thereby increasing right ventricular afterload. In ARDS FRC is considerably reduced and pulmonary vascular resistance is increased at these low lung volumes, a situation that can be reversed by the application of CPAP. Dhainaut has also been able to demonstrate during CPAP both cardiac output and oxygen consumption decrease but that with volume expansion cardiac output increases, while oxygen consumption remains low, suggesting decreased oxygen demand. They have suggested that the explanation for the reduced demand is the reduction of oxygen consumed by the work of breathing following the application of CPAP.

The benefit from application of PEEP to patients with severe ARDS could be viewed using a completing risks analysis, i.e., what is good for the lungs is not necessarily ideal for the heart and cardiovascular system. The use of high levels of PEEP as part of the “open lung” approach may recruit areas of atelectasis and improve both lung compliance and oxygenation, but none of the recently published large randomized trials have shown an improvement in survival (Meade et al. 2008; Mercat et al. 2008). Some insights into why this may be so can be gleaned from the classic study of PEEP in ARDS by Suter et al. published 35 years ago, which is worthy of detailed review (Suter et al. 1975). This was done at a time when there was a considerable amount of debate about the hemodynamic consequences of even a modest amount of PEEP. In this study 15 ventilated normovolemic adult patients with ARDS had PEEP applied in incremental levels of 3 cmH₂O while lung compliance, intrapulmonary shunt, and dead space were measured. In addition, measurements of cardiac output, pulmonary venous saturation, and mixed venous oxygen saturation allowed oxygen transport to be calculated. PEEP was increased until there was a fall in cardiac output, which occurred at levels of between 6 and 18 cmH₂O. They defined “best PEEP” to be the level which coin-

cided with maximum oxygen transport and varied from patient to patient between 0 and 15 cmH₂O (Fig. 53.8).

The important message in this study needs to be relearned 35 years after it was first published, which is that ARDS is a multisystem disease with changes in lung function as its most obvious clinical manifestation. Treatment strategies, which are the ones adopted in clinical trials, have been lung focused emphasizing lung recruitment and minimizing lung distention by using low tidal volumes and high PEEP. Few, if any, have measured any index of the effect on cardiovascular function such as the mixed venous oxygen saturation (SvO₂). At the end of the day, in a disease where multiorgan failure is an invariable component, it is all about oxygen delivery. This is the most important feature of all cardiopulmonary interactions.

53.4 The Effect of Changes in Intrathoracic Pressure in Congenital Heart Disease

53.4.1 Intrathoracic Pressure in Tetralogy of Fallot and Fontan Physiology

Both spontaneous and positive pressure ventilation have important cardiovascular effects in patients with heart abnormalities. One of the most important groups is children with obstructive right heart lesions such as tetralogy of Fallot and tricuspid and pulmonary atresia where changes in ITP can have a dramatic effect on pulmonary blood flow. Important new insights into that have improved our understanding of the cardiorespiratory physiology and how ventilation can change hemodynamics in these patients have come from a series of investigations done by Redington and colleagues. In patients with single ventricle and left atrial isomerism, studied remotely following total cavopulmonary anastomosis, they showed that there is significant augmentation of the pulmonary blood flow Doppler signal during the inspiratory (negative pleural pressure) phase of spontaneous respiration

(Redington et al. 1991) (Fig. 53.9). The application of a Valsalva maneuver resulted in complete obliteration of the PBF, while the large negative pleural pressure produced by a Mueller maneuver gave rise to augmentation of the signal. A study on patients with a Fontan circuit found a 35 % augmentation of PBF during the inspiratory phase of spontaneous breathing (Penny et al. 1991; Penny and Redington 1991). They went on to make some important observations on the effect of changes in intrathoracic pressure and venous return and PBF in patients with tetralogy of Fallot. Diastolic right ventricular dysfunction is a common finding following surgical repair of

severe right ventricular outflow tract obstruction and is characterized by a pulsed Doppler signal showing antegrade pulmonary artery flow during atrial systole accompanied by retrograde flow in the superior vena cava (Kisanuki et al. 1987; Redington et al. 1992). This is due to the fact that right ventricular end-diastolic pressure exceeds pulmonary artery diastolic pressure due to the stiffness of the right ventricle. There is premature opening of the pulmonary valve and the RV acts as a passive conduit between the right atrium and the pulmonary artery. In a study by Cullen et al. (1995) of postoperative tetralogy patients, half had this feature and those that did

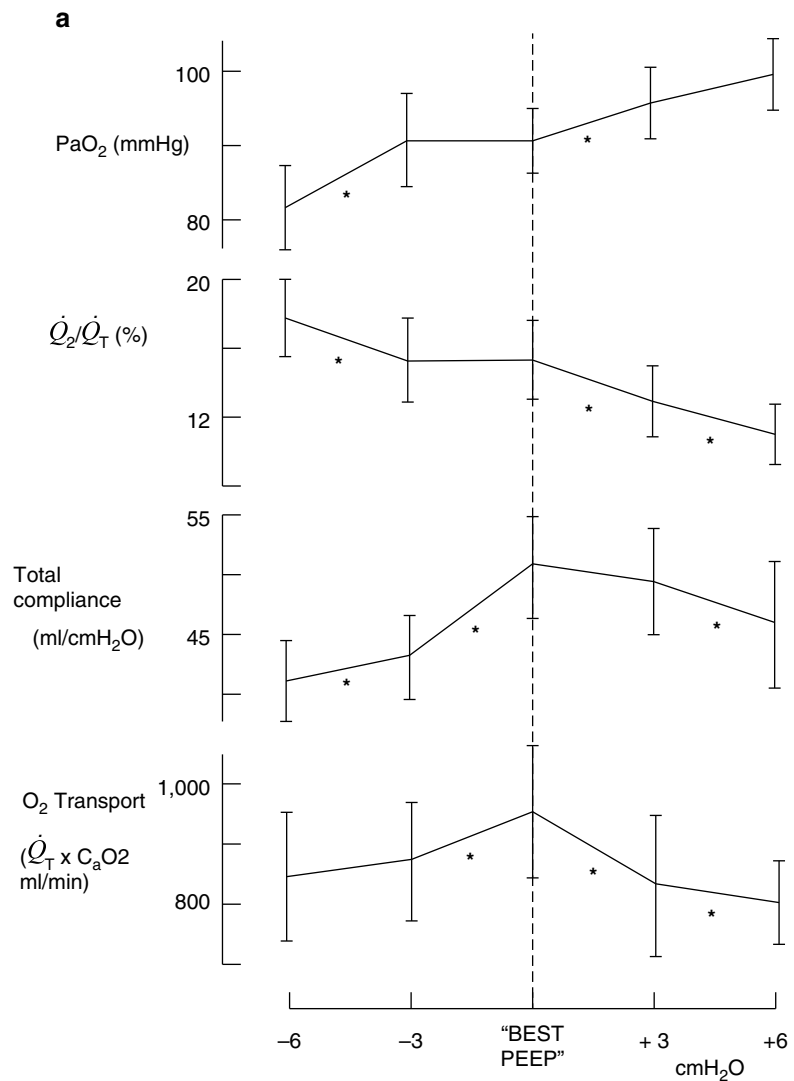
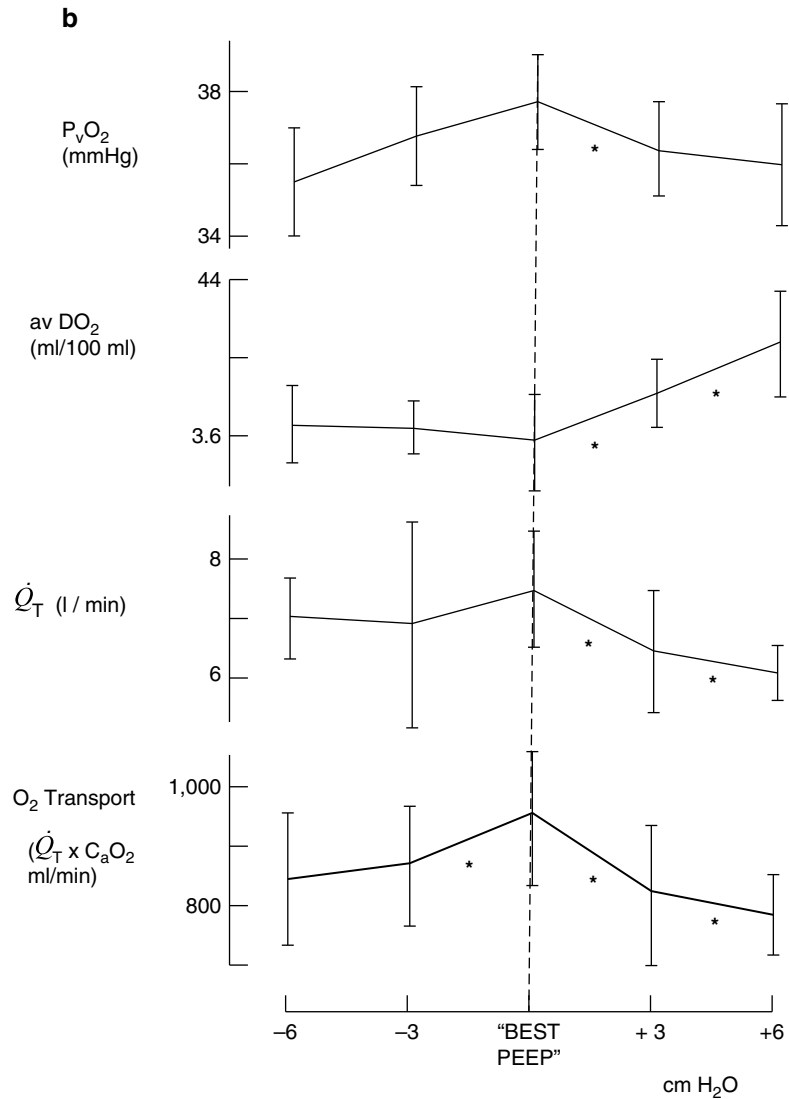
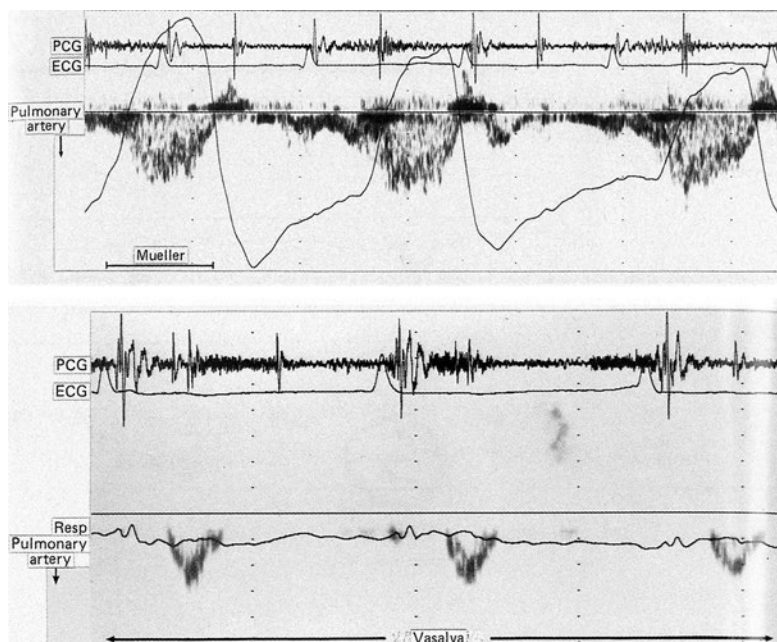


Fig. 53.8 (continued)


had a higher incidence of ascites and pleural effusions and longer durations of ICU stay. He also made the important observation that during the inspiratory phase of positive pressure ventilation, the Doppler signal of antegrade flow in the pulmonary artery was obliterated and there was a decrease in the flow signal across the tricuspid valve (Fig. 53.10). This gave rise to the speculation that negative pressure ventilation (NPV) might actually improve cardiac output and PBF in children following biventricular repairs. In an initial study, Shekerdeman and colleagues compared positive with negative pressure in oth-

erwise healthy children undergoing catheterization and PDA closure with seven children in ICU who had undergone biventricular repair of CHD (Shekerdeman et al. 1997). They found that NPV was associated with a significant increase in cardiac output in the postoperative patients (Fig. 53.11). They did further series of acute studies in 11 patients after repair of tetralogy or the Fontan operation (Shekerdeman et al. 1996). Patients were switched from positive pressure to negative pressure ventilation for 15-min periods while cardiac output, PBF, and oxygen consumption were measured by the Fick equation and

Fig. 53.9 The effect of changes in ITP on pulmonary blood flow in patients following total cavopulmonary connection measured by Doppler. During the Mueller maneuver the flow signal is augmented, while during the Valsalva it decreases (From Redington et al. (1991))



mass spectrometry. NPV was associated with a 46 % increase in PBF, a 48 % increase in stroke volume, and a 4.6 % increase in SVO_2 . Similar to the extended studies they had done in the Fontan patients, they did a series of short-term (15 min) and extended trials of NPV in 23 children who had undergone repair of tetralogy, 8 of whom had restrictive right ventricular physiology (Shekerdemian et al. 1999). These patients were characterized by antegrade diastolic pulmonary artery flow and had a more significant degree of metabolic acidosis compared with their nonrestrictive peers. By the end of 45 min of NPV, pulmonary blood flow had increased by 67 % in the group as a whole, but interestingly the trend to improvement was lower in the restrictive group. The beneficial effect was lost when patients were switched back to PPV.

What are the implications of these studies using negative pressure ventilation for the postoperative management of patients with Fontan and tetralogy with restrictive right ventricular physiology? It is unlikely that NPV will become a standard method for postoperative respiratory support. All these studies were done with patients intubated, anesthetized, and on pressure support ventilation. External negative pressure ventilation requires a significant amount of expertise to oper-

ate efficiently in the postoperative period and cannot be used unless the sternum is intact. However, these studies do demonstrate an important physiological principle, i.e., that all other things being equal spontaneous breathing is a preferred option over positive pressure ventilation in this patient group. The goal should be early weaning and the reestablishment of spontaneous breathing progressing towards early extubation (Shekerdemian et al. 2000) on the assumption that this would have a beneficial effect on venous return and pulmonary blood flow, echoing the comments made by Fontan himself 35 years ago that “respiratory assistance should be stopped early because positive pressure prevents venous return” (Fontan and Baudet 1971). Our current postoperative management strategy for Fontan patients is to extubate in the operating room or, failing that, to leave the patients intubated but start short-acting sedative/analgesic infusions in the operating room prior to transfer to ICU. If there are no bleeding complications, rhythm disturbances, or other factors that would preclude early extubation, the patients have the sedation discontinued and are extubated within 6–8 h of returning from the operating room. If low cardiac output or other postoperative complications prevent this plan from being implemented, then a ventilation strategy based around

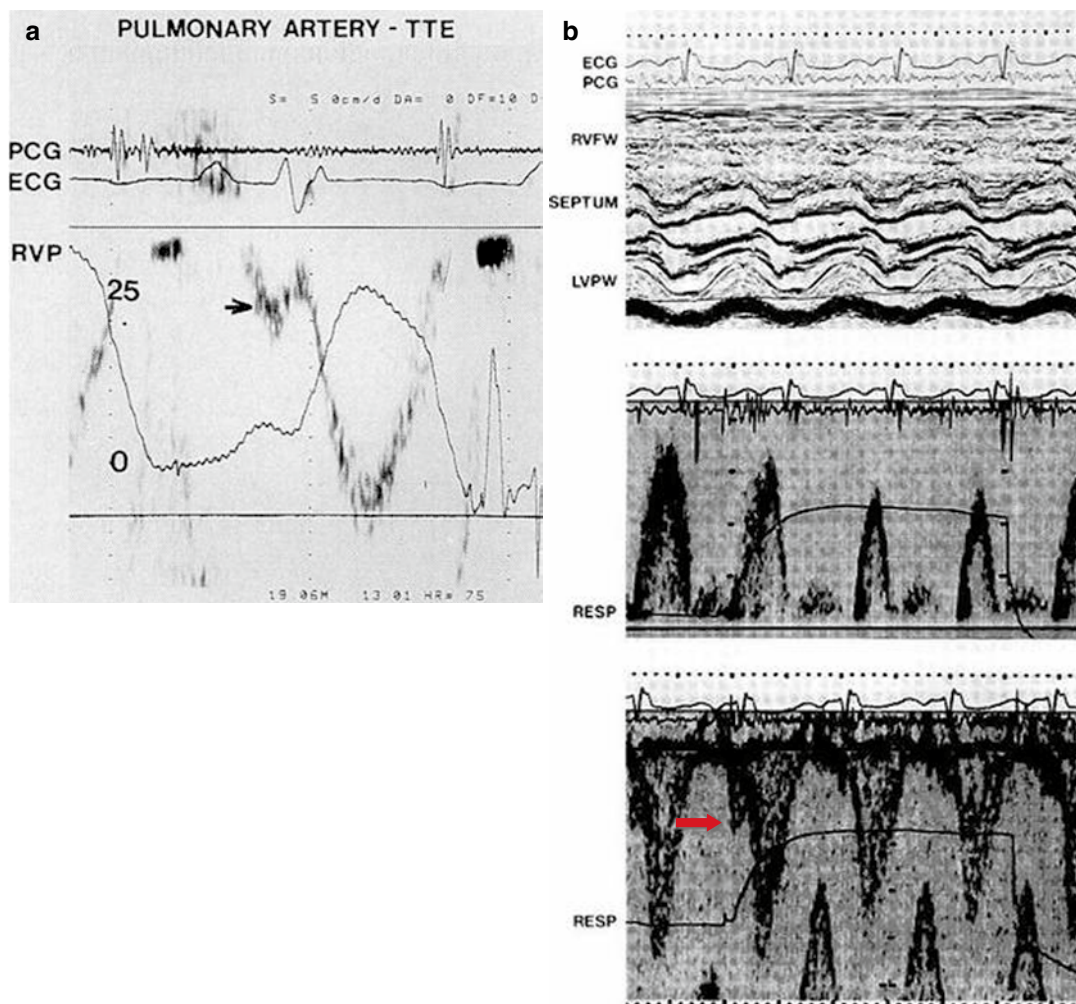


Fig. 53.10 (a, b) Pulmonary artery Doppler flow (a) in a patient with tetralogy of Fallot and restrictive RV physiology demonstrating antegrade PA diastolic flow (arrow) coincident with atrial systole. The effect of positive pressure ventilation on trans-tricuspid flow (b, middle panel)

and pulmonary artery flow (b, lower panel) During the inspiratory phase of positive pressure ventilation, there is diminution of peak velocity (middle figure) and antegrade PA diastolic flow (bottom figure, arrow) (From Cullen et al. (1995))

minimizing mean airway pressures would seem logical.

Attempts have been made to see if high-frequency, low tidal volume ventilation would confer any benefit on cardiac output following the Fontan operation based on the hypothesis that lox ITP would be beneficial. Meliones compared high-frequency jet ventilation (HFJV) with conventional ventilation (CMV), patients being ventilated to the same PaCO_2 levels (27 mmHg) (Meliones et al. 1991). This was achieved with a 50 % lower MAP on jet ventilation and this

resulted in a 25 % increase in cardiac output and a 59 % reduction in PVR. In a second study where high-frequency oscillatory ventilation (HFOV) was compared with CMV at similar (low) MAPs, no difference in cardiac output or PVR was found (Kornecki et al. 2002).

In terms of the implications of these observations outside of specialized cardiac centers, it should be borne in mind that, with increased numbers of children with single ventricle lesions surviving the third-stage reconstruction and into adulthood, there are important messages to be

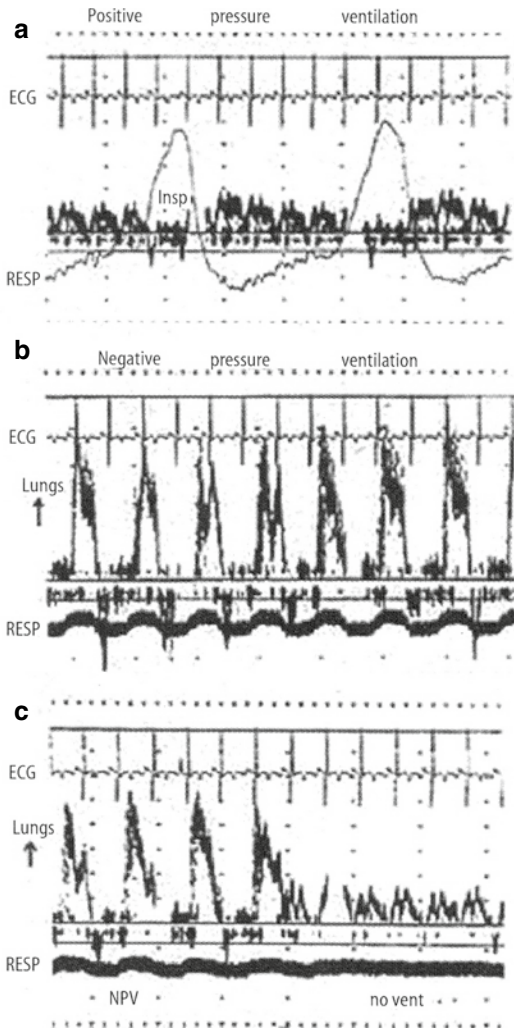


Fig. 53.11 The effect of (a) positive and (b) negative pressure ventilation in a patient after the Fontan operation. During the positive pressure inspiration, antegrade pulmonary artery flow is lost, while there is a marked increase during negative pressure inspiration. The augmentation of pulmonary blood flow was lost when the negative pressure cuirass was removed (c) (From Shekerdemian et al. (1996))

learned from these studies by practitioners administering anesthesia to patients with Fontan physiology, namely, the importance of maintaining adequate filling pressures and using low intrathoracic pressure ventilation (Hosking and Beynen 1992). This was demonstrated in the early days of the Fontan operation before staged reconstruction with the prior placement of the bidirectional cavopulmonary shunt (BCPS).

Patients were operated on who had a high PVR and required very high filling pressures. Military antishock trousers (MAST) were applied over the lower limbs and abdomen in order to augment venous return without using massive amounts of fluid (Heck and Doty 1981). There is also an interesting case report of a cardiac arrest in a Fontan patient where CPR was initially unsuccessful until external abdominal compressions were applied (Tewari and Babu 1994).

53.4.2 Positive Intrathoracic Pressure and the Bidirectional Cavopulmonary Shunt

A second group of patients where there have been important new insights into cardiopulmonary interactions are those following the bidirectional cavopulmonary shunt operation (BCPS), performed as a second stage reconstruction for single ventricle lesions. In this operation, the superior vena cava is disconnected from the right atrium and anastomosed to the pulmonary artery. This places the cerebral and pulmonary circulations in series. Pulmonary blood flow is dependent on venous return from the head, neck, and upper limbs. Oxygenation depends on an adequate transpulmonary pressure gradient between the SVC and the pulmonary capillaries. Typically, the postoperative systemic saturation is in the region of 80 %.

Having excluded the anatomical causes that may be responsible, the traditional therapeutic approach has been, having ensured an adequate filling (right atrial) pressure, to assume that this is a downstream problem due to an increased PVR and to attempt to reduce it by inducing an alkalosis with hyperventilation, with or without inhaled nitric oxide (iNO). However, there is little evidence to show that iNO has any beneficial effect on PVR following a BCPS as measured by an increase in SvO_2 , PaO_2 , or SaO_2 despite a minor decrease in Pa pressure (Adatia et al. 2005). There is also the possibility that the increase in mean airway pressure associated with hyperventilation may actually result in an increase in PVR. One might also draw the conclusion that

the problem does not lie downstream from the pulmonary artery and the focus should shift to in the inflow side of the cavopulmonary connection. Bradley and colleagues reasoned that since hyperventilation, by lowering the PaCO_2 , actually results in a decrease in cerebral blood flow, this might adversely affect PBF and oxygen delivery (Bradley et al. 1998). They studied a series of 13 postoperative BCPS patients (9 hemi-Fontan). Hyperventilation was induced by increasing the respiratory rate while keeping the tidal volume constant. The PaCO_2 fell from 50 to 33 mmHg while pH increased from 7.38 to 7.5. This resulted in a fall in PaO_2 and SaO_2 and an increase in upper body a-v DO_2 . In addition, they measured cerebral blood flow velocity (CBFV) by transcranial Doppler and showed that this decreased with hyperventilation. These findings reversed when patients were changed back to baseline ventilation. The proposed mechanism was an alkalosis-induced cerebral vasoconstriction resulting in lower SVC blood flow. They then reasoned that, since hyperventilation decreased PBF, hypoventilation might actually improve it. In a second series of studies, they induced hypercarbia by decreasing the ventilator rate and compared this with a metabolic alkalosis induced by bicarbonate and ventilation to baseline normocarbia (Bradley et al. 2003). Hypoventilation resulted in improved systemic saturation, PaO_2 , reduced a-v DO_2 , and increased cerebral blood flow velocity. Metabolic alkalosis resulted in no significant change compared with baseline ventilation. In both these studies mean airway pressure changed with the increases and decreases in ventilator rate.

These studies left unanswered whether the improvements in oxygenation and oxygen delivery are due to the hypercarbia increasing total cardiac output or by selectively increasing CBF. There was also the issue of what effect the change in MAP might have had in Bradley's studies. These issues were addressed in a study by Hoskote where hypercarbia was induced by the addition of CO_2 to the inspiratory gas flow of the ventilator while other parameters were unchanged (Hoskote et al. 2004). CBF was measured by near-infrared spectroscopy and transcranial

Doppler, and blood samples were obtained from a jugular venous bulb, PA, and femoral catheters. Patients were studied at PaCO_2 levels of 35, 45, and 55 mmHg and then on return to 40 mmHg. Arterial PaO_2 , SaO_2 , cerebral oxygen saturation, and systemic oxygen delivery increased at PaCO_2 levels of 45 and 55 mmHg compared with 35 mmHg (Figs. 53.12 and 53.13). This beneficial effect was lost when PaCO_2 levels returned to 40 mmHg. Furthermore, hypercarbia resulted in reduced oxygen consumption and decreased arterial lactate concentrations in this patient group (Li et al. 2005). The conclusion from these studies is that hypercarbia post BCPS improves both cardiac output and cerebral blood flow and that hypocarbia has the opposite effect. These studies suggest that the traditional approach to hypoxemia post BCPS of using hyperventilation is not only ineffective but is in fact harmful. The management algorithm for postoperative hypoxemia in these patients should include a diligent search to exclude anatomical obstruction at the level of the cavopulmonary anastomosis and a bubble study to exclude decompressing venous collaterals. The optimum ventilation strategy is moderate hypercarbia (PaCO_2 55 mmHg) with a pH in the region of 7.35, proceeding to early extubation with the expectation that the combination of spontaneous respiration and mild hypercarbia will augment PBF.

53.4.3 Positive Pressure Ventilation and Ventricle Lesions with Duct-Dependent Systemic Perfusion or Systemic to Pulmonary Artery Shunts

The management of mechanical ventilation in infants with functionally single ventricle lesions presents some unique challenges. Instead of two ventricles in series, these patients have parallel circulation supported by a single pumping chamber. The objective is to achieve a 1:1 distribution of systemic to pulmonary blood flow, which is consistent with an arterial saturation of 75–80 %, assuming that the pulmonary venous saturation is >95 %. Reductions in PVR induced by hyperoxia

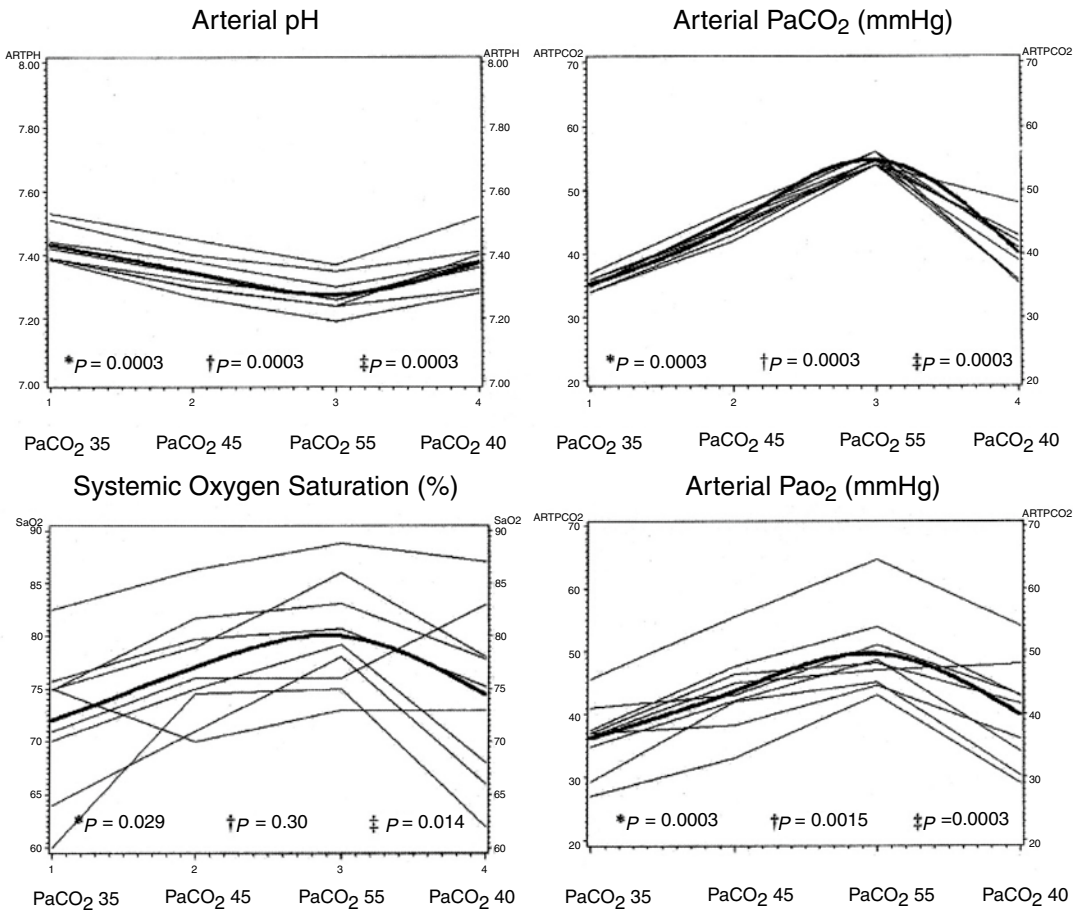


Fig. 53.12 Arterial pH, PaCO₂, SaO₂, and PaO₂ associated with various levels of hypercarbia in nine patients following BCPS. The *lines* represent individual patients,

while the *bold line* indicates the mean value (From Hoskote et al. (2004))

or alkalosis will lead to pulmonary overcirculation and reduced systemic oxygen delivery to other vital organs. This can result in end-organ damage such as cerebral ischemia and necrotizing enterocolitis. Methods to optimize systemic output and control PBF in this situation have included the induction of a moderate degree of hypercarbia with a respiratory acidosis by adding inspiratory CO₂ and alveolar hypoxia by decreased FiO₂ (<0.21) in the inspiratory gas mixture. The latter two strategies have been compared in infants with hypoplastic left heart syndrome (Ramamoorthy et al. 2002; Tabbutt et al. 2001). These studies have shown that the use of an FiCO₂ of 3 % compared with an FiO₂ of 17 % resulted in better oxygen delivery and cerebral oxygen saturation.

These data would suggest that the use of respiratory acidosis is a better method of controlling PBF than using hypoxic gas mixtures. This has been highlighted by a recent study by Taeed et al. (2001) which showed that there is a high incidence of pulmonary venous desaturation in infants after the Norwood procedure. Since a key part of the management strategy for limiting PBF in the postoperative period has been to limit the FiO₂ to 0.21 while assuming a saturation of >95 % in pulmonary venous blood with an SaO₂ of 75–80 % indicating a 1:1 ratio of systemic to PBF, the assumptions behind this must now be questioned. Decreasing the FiO₂ in this situation may result in hypoxemia and reduced oxygen delivery. Therefore, the preferred strategy should be to use

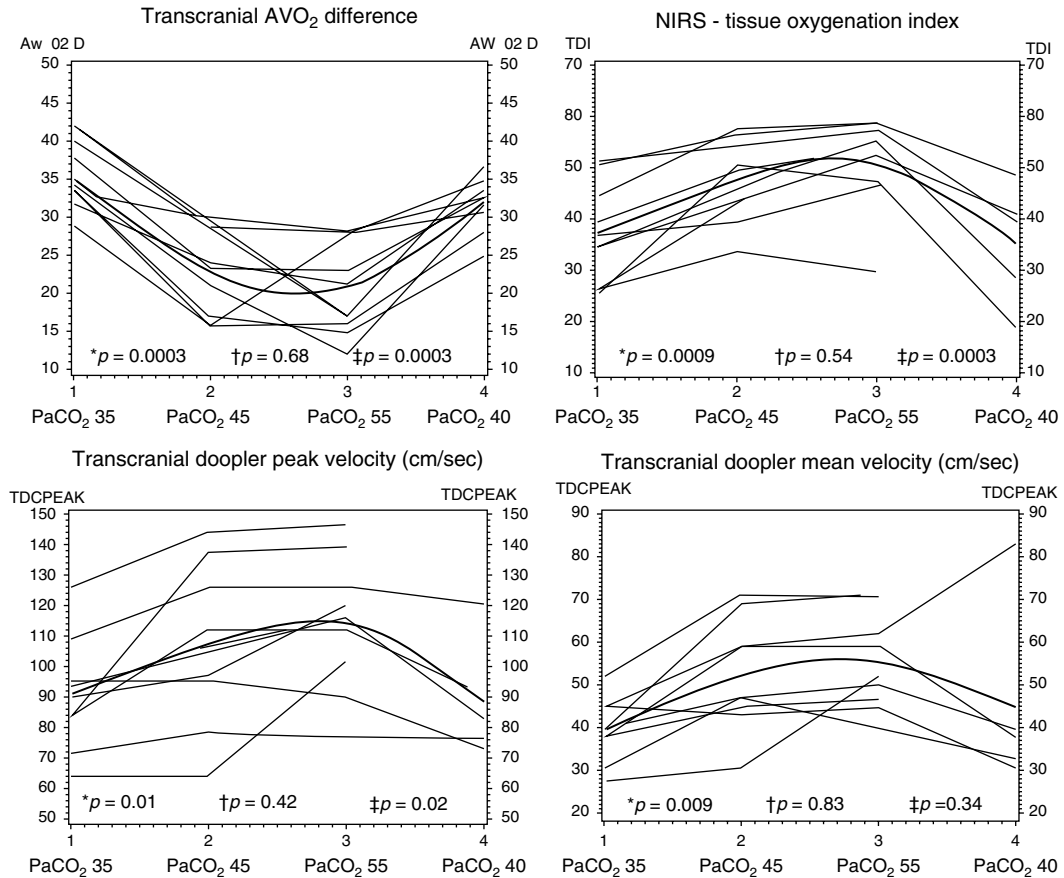


Fig. 53.13 Transcranial arteriovenous oxygen difference, NIRS tissue oxygenation index, peak transcranial Doppler velocity, and mean transcranial Doppler velocity

at various levels of hypercapnia. The *lines* represent individual patients. (From Hoskote et al. (2004))

a respiratory acidosis (pH 7.3) to increase PVR while maintaining a PaO₂ of 35–40 mmHg.

53.4.4 Positive Pressure Ventilation in Left to Right Intracardiac Shunts

Children with congenital heart lesions associated with left to right shunts frequently have respiratory symptoms due to increased PBF. The bronchiolar narrowing due to the high flows and pulmonary venous pressure produce interstitial and alveolar edema. Hordof et al. (1977) have described clinical and radiological manifestations of peripheral airway obstruction in infants with VSD associated with high pulmonary to

systemic flow ratios, which regressed with closure of the defect. Schindler et al. (1995) have demonstrated that rises in pulmonary artery pressure in the postoperative period are associated with increases in measured airway resistance and that there is increased smooth muscle in the airways of these children. These observations may explain the finding of sudden episodes of bronchospasm commonly seen in patients who develop rapid rises in pulmonary artery pressure following corrective cardiac surgery for lesions such as VSD and AV septal defect. It is likely that some of the bronchoconstrictor response seen in pulmonary hypertension may be mediated, at least in part, by the leukotriene products of arachidonic metabolism. Leukotrienes C₄ and D₄, known as mediators of bronchoconstriction in

asthma, have been shown to be present in large quantities in the lung lavage fluid of infants with persistent pulmonary hypertension of the newborn (PPH) (Stenmark et al. 1983).

There are also changes in lung compliance seen in congenital cardiac disease (Bancalari et al. 1977; Howlett 1972; Wallgren et al. 1960). Bancalari et al. (1977) have found that both total and specific lung compliance were significantly lower in children with congenital heart disease in situations where there was increased pulmonary blood flow, compared to lesions with a normal or decreased pulmonary blood flow. When pulmonary blood flow was increased but pulmonary artery pressure was normal, compliance was unchanged, suggesting that it was the pressure level rather than the increased flow within the lung which actually caused the alteration in compliance. Decreased pulmonary compliance has also been described in newborn infants with PPHN (Yeh and Lilien 1981). It is these changes in compliance that are responsible for the increased respiratory rate and decreased tidal volume seen during spontaneous respiration in children with left to right intracardiac shunts (Lees et al. 1968). In the infant and small child with a highly compliant chest wall, this is frequently associated with chest wall retraction and intercostal recession. With increasing age these become less prominent as pulmonary vascular resistance rises secondary to increased flow and left to right shunting diminishes. These respiratory symptoms are more likely to occur after the first 2 months of life, when the pulmonary vascular resistance drops and left to right shunting increases and before the end of the first year, when the airways become more cartilaginous and less liable to compression (Lister and Pitt 1983).

The use of positive pressure ventilation in children with heart failure secondary to increased PBF is effective in reducing respiratory muscle work and oxygen consumption. However, hyperventilation-induced respiratory alkalosis, together with hyperoxia, may actually increase PBF and cause worsening of pulmonary edema. Therefore, tidal volume and rate should be adjusted to produce a normal pH or

mild respiratory acidosis together with a level of FiO_2 sufficient to produce a SaO_2 of 85–90 %. The application of PEEP may also be effective in limiting PBF.

53.5 Cardiopulmonary Interactions in Acquired Heart Disease

53.5.1 Positive Pressure Ventilation and Heart Failure

The cardiac effects of the negative pleural pressure during spontaneous respiration have been discussed previously. Whether the increase in afterload on the left ventricle becomes hemodynamically significant depends on the underlying pump function. If ventricular function is normal, the negative intrathoracic pressure associated with spontaneous breathing will result in little or no significant hemodynamic change (Polianski et al. 1986). However, some of the studies that have examined the magnitude of the afterload effect produced by increased negative or positive intrathoracic pressure have tended to underestimate its significance because of different methods of measuring afterload. Considering the left ventricle in isolation, in situations where there is a major change in intrathoracic pressure associated with increasing negative intrapleural pressures secondary to lung disease or positive intrapleural pressures secondary to mechanical ventilation, aortic pressure does not reflect left ventricular afterload. Buda et al. (1979) in a study of the effects of Valsalva and Mueller maneuvers on left ventricular function in humans found that LV ejection fraction decreased despite an increase in left ventricular volume and a decline in arterial pressure. When arterial pressures were corrected for changes in intrapleural pressure, they correlated better with left ventricular end-systolic volumes than with uncorrected arterial pressures. These findings suggested that negative intrathoracic pressure affects left ventricular function by increasing left ventricular transmural pressures and thus afterload. Physiologically more consistent function curves for the left ventricle were obtained when transmural pressure was used for the pressure load

for left ventricular ejection. If the left ventricular filling pressure is unchanged, similar changes in left ventricular afterload can result from either reducing aortic pressure by vasodilator therapy or increasing intrathoracic pressure if the net result is no change in transmural pressure.

Although acute impairment of left ventricular ejection associated with the generation of large negative intrathoracic pressures has been demonstrated when ventricular function is normal (Scharf et al. 1979a, b, 1981, 1987), it is only comparatively recently that the clinical significance of this has been realized in the presence of left ventricular failure. Rasanen et al. (1984) showed that changing from spontaneous to positive pressure breathing in patients with myocardial infarction resulted in a decrease in the pattern of injury seen on the EKG and subsequently confirmed that the myocardial sparing only occurred when the negative swings in intrathoracic pressure were abolished (Rasanen et al. 1985a, b). Similarly, Beach et al. (1973) has described a series of adult patients with left ventricular failure supported with positive pressure ventilation who could not tolerate the wean to spontaneous ventilation until left ventricular function was improved with inotropic support. However, raised intrathoracic pressure does have the potential to adversely affect contractility in the setting of marginal coronary blood flow. PEEP has been reported to cause a decrease in myocardial blood flow in experimental animals (Cassidy et al. 1982; Manny et al. 1978), and Tittley et al. (1985) has shown that the application of 15 cmH₂O after coronary artery bypass surgery resulted in small but measurable amounts of markers of marginal coronary perfusion in half the patients studied without a change in ventricular function. Based on these findings we can conclude that in patients with overt cardiac failure or borderline left ventricular function, the increased afterload associated with the negative intrathoracic pressure generated during spontaneous respiration may result in worsening heart failure. Furthermore, in situations where pulmonary edema develops following myocardial infarction, the pulmonary venous congestion and alveolar flooding that occur lead to a fall in lung compliance which translates into increased

respiratory work and greater negative intrathoracic pressure (Naughton et al. 1995b). In this situation respiratory muscle work may contribute significantly to inadequate oxygen delivery and lactic acidosis. Positive intrathoracic pressure with the use of continuous positive airway pressure (CPAP) may result in rapid improvement in the situation with interruption of the cycle of increasingly negative intrathoracic pressure producing an ever-decreasing lung compliance. Therefore increasing intrathoracic pressure, far from adversely affecting cardiac output, as has been widely assumed for many years, may in fact enhance cardiac performance as long as filling pressures are adequate (Grace and Greenbaum 1982; Mathru et al. 1982). The extreme example of this would be the discovery that during ventricular fibrillation where there is no left ventricular function output, raising pleural pressure by coughing results in forward blood flow out of the thorax by a combination of the direct effect on the heart and great vessels as well as decreased afterload. This phenomenon is commonly referred to as “cough CPR” (Criley et al. 1976).

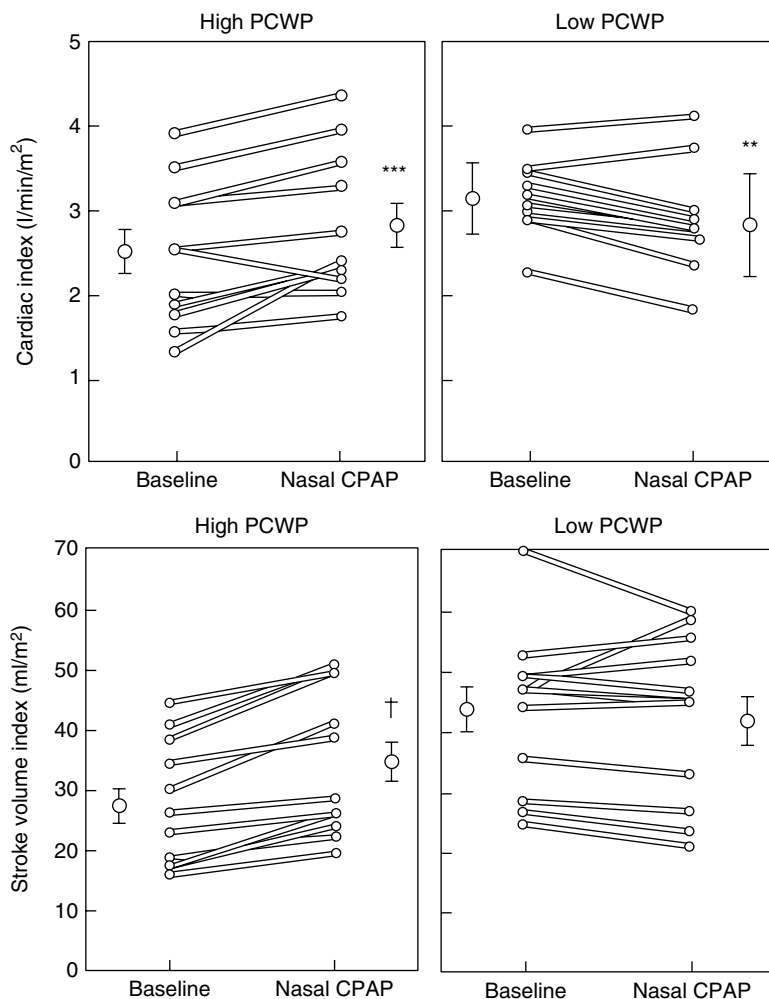
Some of the most interesting insights into the effects of elevations in intrathoracic pressure in the setting of left ventricular failure come from the work of Pinsky and colleagues (1983, 1990a, b, 1994a, b, 1997). In their animal model left ventricular failure was induced with large doses of beta blockade while adequate venous return was maintained by volume infusion. In order to study the effects of large increases in intrathoracic pressure on cardiac function without overdistending the lung and causing increased pulmonary vascular resistance and pulmonary barotrauma, they reduced thoracic cage compliance by applying a thoracoabdominal binder (Pinsky et al. 1983). Tidal volumes of 35 ml/kg were used to produce a “phasic high intrathoracic pressure support” ventilation (PHIPS). This study showed that there was an improvement in both left and right ventricular function curves with increased intrathoracic pressure, a finding that they attributed to a decrease in left ventricular wall stress analogous to the use of vasodilator therapy in congestive heart failure. The same technique was applied to a group of patients with cardiogenic

shock, and when conventional ventilator settings were changed to the PHIPS technique, there was an improvement in cardiac output and mean arterial pressure (Pinsky and Summer 1983). Although it is clear that these large changes in intrathoracic pressure augment cardiac output in the failing heart, the mechanism responsible for this action is a balance between the effect on left ventricular preload and afterload. Large changes in lung volume will affect intra- and extra-alveolar blood volume (Brower et al. 1985) and result in increased forward flow. At the same time increased intrathoracic pressure will reduce left ventricular afterload. These differing mechanisms were studied in a further series of experiments by Pinsky et al. (1985) where they varied respiratory frequency, percent inspiratory time, and swings in intrathoracic pressure using a jet ventilator under normal conditions and during acute left ventricular failure. They found that despite a decrease in transmural left atrial pressure, a rise in intrathoracic pressure resulted in an increase in left ventricular stroke volume. Furthermore this increase in stroke volume continued until a lower limit of left atrial pressure was reached after which there was no further augmentation of left ventricular stroke volume. This demonstrates that when cardiac function is reduced and filling pressures are elevated, an increase in intrathoracic pressure can result in an increase in cardiac output despite a fall in filling pressures. However this augmentation becomes limited once a critical value is reached when cardiac output becomes again dependent upon filling pressures. A similar effect has been described when intrathoracic pressure is increased by the addition of PEEP in the setting of left ventricular dysfunction in humans. The application of PEEP in this situation does not result in a decrease in cardiac output until the filling pressure fell below 15 mmHg (Grace and Greenbaum 1982).

These data and data from human studies which show enhanced cardiac performance with increased pressure intrathoracic pressure in the setting of cardiogenic shock (Rasanen et al. 1984; Rasanen et al. 1985b) would suggest that this aspect of the beneficial effect of increased intrathoracic pressure on left ventricular perfor-

mance is influenced by preload, being least beneficial when left ventricular filling was reduced and most marked where left ventricular filling pressures were elevated. It has also become evident that hemodynamic changes that occur with increased intrathoracic pressure vary according to different phases in the cardiac cycle. This has been demonstrated in further studies by Pinsky et al. (1986) where positive pressure ventilation was linked to the cardiac cycle by the use of a jet ventilator in animals with left ventricular failure. When positive pressure was timed to occur early in diastole in normal animals, left ventricular stroke volume was decreased, whereas when it was timed to coincide with early systole, there was no effect. In addition it was noted that positive pressure was phased with early diastole, the reduction in stroke volume of the right ventricle preceded that of the left ventricle by one to two heartbeats, suggesting that the cause of the reduction was due to a reduced venous return. In the animals with left ventricular failure, increased intrathoracic pressure in phase with systole increased left ventricular stroke volume compared to diastole, although the increased intrathoracic pressure in either phase was associated with increased stroke volume when compared to apnea. These investigators then compared the hemodynamic effects of increases in intrathoracic pressure synchronized to early and late systole. They found that while increased intrathoracic pressure in both phases of the systolic cycle was associated with an increase in stroke volume when compared to apnea, early systolic phase ventilation resulted in an increase in stroke volume without a change in aortic pressure, while late systolic ventilation increased both stroke volume and pressure. These findings would suggest that positive pressure ventilation synchronized with early cardiac systole allows for left ventricular ejection into a volume-depleted thoracic aorta. They have recently applied these principles in the clinical arena for the ventilatory management of patients with severe congestive cardiomyopathy who are undergoing heart transplantation (Pinsky et al. 1987) when they compared the effects of high-frequency jet ventilation (HFJV) synchronized with cardiac systole, HFJV asynchronous

Fig. 53.14 The effect of nasal CPAP on cardiac output in a series of adult patients with congestive heart failure. Individual data for patients with high and low capillary wedge pressures (PCWP) are shown together with the grouped data. With the application of CPAP, cardiac index rose 10 of 11 high PCWP patients, while it decreased in 9 of 11 in the low PCWP group. $**p < 0.025$ and $***p < 0.001$ compared with baseline (From Bradley et al. (1992))



with the cardiac cycle, and conventional ventilation at similar levels of intrathoracic pressure. They found that changing to synchronous HFJV was associated with an increase in cardiac output compared to the other modes of ventilation.

53.5.2 The Use of Noninvasive Continuous Positive Airway Pressure in Heart Failure

One of the most important advances in the treatment of congestive heart failure in the past decade has been the use of noninvasive ventilation in the form of either CPAP or BiPAP (Naughton et al. 1994, 1995a, b, c; Bersten et al. 1991; Bradley et al.

1992; Faccenda et al. 2001; Kaneko et al. 2003; Mehta et al. 1997, 2000; Sin et al. 2000; Tkacova et al. 1997). The predominant hemodynamic effect of increased intrathoracic pressure will be due to changes in preload if contractility and circulating volume are normal, whereas in situations of reduced left ventricular function, where filling pressures are frequently elevated, the principal hemodynamic change will be changes in left ventricular wall stress (afterload). This has been confirmed in human studies where nasal CPAP has been used to treat adult patients with congestive heart failure. The application of 5 cmH₂O in patients with congestive cardiac failure and a PCWP greater than 12 mmHg resulted an increase in the measured cardiac output while it remained unchanged or fell in patients where car-

diac failure was associated with a normal or low filling pressure (Bradley et al. 1992) (Fig. 53.14). A further study where 5, 7.5, and 10 cmH₂O were applied showed a similar beneficial effect in that left ventricular systolic transmural pressure (afterload) fell (Naughton et al. 1995b). The same group has been able to demonstrate improved left ventricular function and symptomology in a randomized controlled trial of nocturnal nasal CPAP in patients with heart failure associated with Cheyne-Stokes respiration and central sleep apnea (Naughton et al. 1995a). Other randomized trials in adults have shown a reduction in the need for intubation (Bersten et al. 1991) in the degree of mitral regurgitation and ANF levels (Tkacova et al. 1997), decreases in respiratory muscle effort (Lenique et al. 1997), improved left ventricular end-systolic dimensions, and improved LV ejection fraction as well as reduced heart rate and blood pressure (Kaneko et al. 2003). There are no equivalent studies in children. However, the use of CPAP and BiPAP has become widely accepted in pediatric practice for the treatment of myocarditis and cardiomyopathy. These patients have severely reduced ventricular function and increased respiratory distress due to pulmonary edema. The use of noninvasive ventilation avoids the need to administer the sedative/anesthetic drugs which would be required for endotracheal intubation with the precipitate drop in cardiac output that it would produce. The dual effect of decreasing respiratory work at the same time as decreasing the LV afterload often leads to a dramatic symptomatic improvement.

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Part XIX

Mechanical Ventilation in Infection, Sepsis and Organ Failure

Andrew C. Argent and Niranjan “Tex” Kissoon

Educational Aims

- Consider an approach to ventilation in patients with sepsis of all kinds.
- Discuss some of the possible modes of ventilatory support, with particular attention to their potential use in patients with sepsis or organ failure.
- Consider anaesthesia for initiation of invasive ventilation in patients with sepsis.
- Define the goals of ventilation in patients with severe sepsis or organ failure.
- Review the cardiovascular implications of ventilatory support in patients with sepsis.
- Consider processes to minimize lung damage during ventilation.
- Consider specific infections and some of the implications for ventilation.
- Briefly address issues of infection control.

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54.1 Introduction

Each day thousands of children across the world die as a result of infection. Sepsis, severe sepsis and septic shock represent a continuum of increasing severity for which present definitions are not wholly satisfactory (Levy et al. 2003; Brilli and Goldstein 2005). The term sepsis refers to the presence of an infection caused by a microbe that invades tissue, fluid or a body cavity that is normally sterile, plus the presence of clinical and/or laboratory evidence of the systemic inflammatory response syndrome (SIRS, temperature or leucocyte abnormalities and abnormal vital signs) (Goldstein et al. 2005). When sepsis is complicated by multi-organ failure, it is regarded as severe, while septic shock is diagnosed when sepsis coexists with a state of acute circulatory failure (Levy et al. 2003).

Sepsis may be related to a wide variety of different microorganisms (Goldstein et al. 2005) (including bacteria, viruses, protozoa, rickettsiae and fungi) with many different toxins and pathogenetic mechanisms. In addition, the clinical features of infection in a patient may vary due to a variety of factors including the genetic predisposition (Opal 2007); infective dose, route of infection and virulence factors of the particularly organism; possible co-infections; and underlying illness, nutritional status, medication; and the organs affected by the infection (and responses) (Opal 2005).

Thus septic patients who require ventilation make up a very broad spectrum of contexts and specific situations. The indications for and the goals of ventilation may therefore vary considerably in patients (Table 54.1).

Table 54.1 Definitions of systemic inflammatory response syndrome (SIRS), infection, sepsis, severe sepsis and septic shock

Category	Features	Criteria
<i>Systemic inflammatory response syndrome (SIRS)</i>	The presence of at least two of the following four criteria, one of which must be abnormal temperature or leucocyte count	Core temperature of $>38.5^{\circ}\text{C}$ or $<36^{\circ}\text{C}$ Tachycardia, defined as a mean heart rate >2 SD above normal for age in the absence of external stimulus, chronic drugs or painful stimuli or otherwise unexplained persistent elevation over a 0.5- to 4-h time period, OR, for children <1 year old, bradycardia, defined as a mean heart rate <10 th percentile for age in the absence of external vagal stimulus, β -blocker drugs or congenital heart disease or otherwise unexplained persistent depression over a 0.5-h time period Mean respiratory rate >2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or general anaesthesia Leucocyte count elevated or depressed for age (not secondary to chemotherapy-induced leucopenia) or $>10\%$ immature neutrophils
Infection	A suspected or proven (by positive culture, tissue stain or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection	Evidence of infection includes positive findings on clinical exam, imaging or laboratory tests (e.g. white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash or purpura fulminans)
Sepsis	SIRS in the presence of or as a result of suspected or proven infection	
Severe sepsis	Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions	<i>Cardiovascular dysfunction</i> See below under septic shock <i>Respiratory</i> $\text{PaO}_2/\text{FiO}_2 < 300$ in the absence of cyanotic heart disease or pre-existing lung disease OR $\text{PaCO}_2 > 65$ Torr or 20 mmHg over baseline PaCO_2 OR Proven need or $>50\%$ FiO_2 to maintain saturation $>92\%$ OR Need for nonelective invasive or noninvasive mechanical ventilation <i>Neurologic</i> Glasgow Coma Score <11 OR Acute change in mental status with a decrease in Glasgow Coma Score >3 points from abnormal baseline <i>Haematologic</i> Platelet count $<80,000/\text{mm}^3$ or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic haematology/oncology patients) OR International normalized ratio >2 Renal Serum creatinine >2 times upper limit of normal for age or twofold increase in baseline creatinine Hepatic Total bilirubin >4 mg/dL (not applicable for newborn) OR ALT 2 times upper limit of normal for age

Table 54.1 (continued)

Category	Features	Criteria
Septic shock	Sepsis and cardiovascular organ dysfunction as defined	Despite administration of isotonic intravenous fluid bolus ≥ 40 ml/kg in 1 h Decrease in BP (hypotension) < 5th percentile for age or systolic BP < 2 SD below normal for age OR Need for vasoactive drug to maintain BP in normal range (dopamine > 5 $\mu\text{g/kg/min}$ or dobutamine, epinephrine or norepinephrine at any dose) OR Two of the following: - Unexplained metabolic acidosis: base deficit > 5.0 mEq/l - Increased arterial lactate > 2 times upper limit of normal - Oliguria: urine output < 0.5 ml/kg/h - Prolonged capillary refill > 5 s - Core to peripheral temperature gap > 3 $^{\circ}\text{C}$

From Goldstein et al. (2005)

54.2 The Nature of Ventilatory Support

Strategies for assisting ventilation include endotracheal intubation and positive pressure ventilation and recently several other modes including noninvasive techniques.

Ventilatory support using high-flow humidified nasal oxygen has been introduced into neonatal practice for respiratory support. There are limited reports of its use in older children with respiratory distress (Spentzas et al. 2009; McGinley et al. 2009). There are a number of commercial systems available. There is considerable variability in the pressures and flows delivered to infants with these systems (Dani et al. 2009; Lampland et al. 2009), and it is suggested that pressure limitation devices should be incorporated (Lampland et al. 2009). More research is required before these can be recommended for respiratory support in children (Randolph 2009) with acute respiratory distress.

Noninvasive ventilation has been attempted in children with acute respiratory failure due to a wide variety of conditions (Teague 2005) including neuromuscular conditions (Katz et al. 2004; Reddy et al. 2004; Hartmann et al. 1994), asthma (Haggenmacher et al. 2005; Ram et al. 2005) as

well as acute respiratory failure due to infections (Prado et al. 2005; Piastra et al. 2004; Fortenberry et al. 1995).

After an initial report of nCPAP in an infant with apnoea related to RSV infection (McNamara and Sullivan 1997), Thia et al. (2008) demonstrated that nCPAP administered to infants with bronchiolitis and hypercapnia was associated with significant improvement.

A report on 14 patients from Chile (Prado et al. 2005) showed that nCPAP or BiPAP administered via nasal mask in acute respiratory failure due to infection was associated with significant improvement and that most children did not need invasive ventilation.

A recent Cochrane review of negative pressure ventilation in acute respiratory failure (Shah et al. 2005) concluded that there was not enough evidence available to make a recommendation as to its clinical applicability.

Thus it may be possible to use conventional or noninvasive (including nCPAP, BiPAP and mask) ventilation in children with acute respiratory failure related to infection. Unfortunately firm recommendations cannot be made until challenges in terms of masks (including fit), indications and techniques are elucidated (Teague 2005; Loh et al. 2007) and proposed predictors of success (Bernet et al. 2005) confirmed.

54.3 Initiation of Ventilation

Anaesthesia for endotracheal intubation for conventional ventilation is essential, but there is considerable controversy regarding the optimal agents for anaesthesia in acute sepsis (Zelicof-Paul et al. 2005). Selection of appropriate agents will depend on experience and training.

54.4 Drugs for Intubation

Etomidate has been used in a number of studies, but there remains considerable concern regarding possible adrenal suppression following its use in sepsis (Zed et al. 2006; Zuckerbraun et al. 2006). It does however create favourable conditions for intubation (Zelicof-Paul et al. 2005) and is less likely to cause hypotension than agents such as midazolam (Choi et al. 2004).

Ketamine has been used extensively in many settings with a very low complication rate (Melendez and Bachur 2009; Jankiewicz and Nowakowski 1991) and is an agent of choice in many emergencies, while propofol and thiopentone have been used with some success.

54.4.1 Use of Atropine

There is a theoretical benefit for giving atropine when manipulating the airway of infants under 1 year of age due to their disproportionate predominance in vagal tone coupled with a relatively greater dependency on HR for cardiac output (Rothrock and Pagane 2005). However recent evidence suggests that it may be unnecessary (Brown et al. 2008) when ketamine alone is used for anaesthesia. Most bradycardias are due to hypoxia or are a transient vagally mediated reflex response that resolves spontaneously. In special circumstances, such as infants less than 1 year of age, atropine is still considered an option by some practitioners especially prior to a second or repeat dose of succinylcholine.

54.4.2 Use of Paralytic Agents

The choice of agent for paralysis in intubation under emergency conditions remains

controversial. Recent reviews of the adult literature have concluded that there is no benefit to rocuronium and that succinylcholine remains the safest agent (Perry et al. 2008). In the 1990s reviews of the use of succinylcholine vs. rocuronium concluded that succinylcholine remained the recommended choice although this was essentially a matter of personal preference (Robinson et al. 1996; Weir 1997). There have been concerns about the possibility of hyperkalaemic cardiac arrest in the setting of undiagnosed neuromuscular disease. A recent paediatric review (Ching and Baum 2009) has concluded that rocuronium may be a safer agent for use in emergency intubation in children.

A significant concern that has been raised recently (Kendrick et al. 2009) is that the duration of action of agents such as rocuronium or atracurium is significantly longer than that of etomidate. Thus patients who are intubated using the combinations of etomidate and rocuronium or atracurium should receive sedation after intubation to avoid the possibility of awareness while paralysed.

54.5 The Goals of Ventilation

Mechanical ventilation in respiratory failure has been one of the core functions of intensive care since the earliest days of the speciality (Grenvik and Pinsky 2009). The goals of mechanical ventilation have primarily been focused on the maintenance of acceptable blood gases in patients with failure of the respiratory system, but there is also a considerable body of literature related to cardiopulmonary interactions and the effect of mechanical ventilation on cardiovascular function (Bronicki and Anas 2009).

Essentially the goals of ventilation in sepsis and organ failure could be summarized as:

Maintenance of blood gas values that are appropriate to the overall management of the patient (taking into account the effects of sepsis of all organ systems)

Optimization of cardiovascular function

Minimizing damage to the lungs and the respiratory system

Minimizing deleterious effects on other organ systems

Table 54.2 Tissues oxygen delivery problems in sepsis

Blood oxygen content	Haemoglobin	Concentration often low (may be haemolysis as part of the syndrome); may be development of methaemoglobinaemia in specific situations
	Red cell function	May be abnormal as a result of sepsis; in conditions such as sickle cell disease may be exacerbation of abnormalities; transfused blood cells may have abnormal function (Sakr et al. 2007)
Cardiac output	Low in most shocked paediatric patients	Hypovolaemia is very common in paediatric sepsis
		Low cardiac output related to high systemic vascular resistance may be very common May be affected by pulmonary hypertension in young infants
Organ perfusion	Low in many situations	Raised pressure within organs (kidney), spaces (intracranial, intra-abdominal); may reduce perfusion
Tissue perfusion	Microvascular dysfunction	Multiple components of microvascular dysfunction have been described in sepsis and may affect tissue oxygen delivery (Bateman et al. 2003)

The priorities of ventilation in sepsis, from the immediate resuscitation at the time of presentation through the recovery phases of the illness, may differ as the physiology changes. Thus acceptable goals will depend on the stage of the illness.

54.5.1 Acceptable Blood Gas Values

It has been generally accepted that mechanical ventilation in patients with respiratory disease should not always be aimed at the maintenance of normal blood gas values, and recent reviews refer to both permissive hypoxaemia (Cheifetz and Hamel 2006) and hypercapnia (Hickling 2002) and even to therapeutic hypercapnia (Laffey et al. 2000, 2004a; Kavanagh and Laffey 2006).

54.5.1.1 Oxygenation

Tissue oxygen delivery in sepsis may be complex and is affected by the interrelationship of multiple factors (Table 54.2). Optimal oxygen delivery globally or to specific organs is important (particularly in the setting of organ failure).

On the other hand, it is possible that high oxygen concentrations may be problematic, particularly if there are deficiencies in antioxidant defences (Salvemini and Cuzzocrea 2002) which may occur in several settings, including malnutrition.

Deleterious effects of high oxygen concentrations on the lung have been well documented for many years (Pagano and Barazzzone-Argiroffo 2003).

There is considerable animal evidence that high inspired oxygen concentrations in combination

with mechanical ventilation may be related to increased pulmonary inflammation and lung damage (Sinclair et al. 2004; Altemeier and Sinclair 2007). Sinclair et al. also showed that in rabbit model ventilation with moderate tidal volumes using 50 % oxygen (previously regarded as relatively safe) was associated with significant lung damage as compared to ventilation with room air (Sinclair et al. 2004). Experience in neonatology (Ehlert et al. 2006) has also highlighted the deleterious effects of high tidal volumes and hyperoxia.

Apart from effects on the lung, ventilation with high oxygen concentrations adversely affects alveolar macrophage and other immune functions (Baleeiro et al. 2003, 2006) and increases mortality from *Legionella pneumophila* (Tateda et al. 2003) in animal models.

Studies on the effect of hyperoxia on surgical site infections and outcomes following major surgery have yielded conflicting results (Pryor et al. 2004; Greif et al. 2000).

The effects of high oxygen concentrations on tissue in the setting of sepsis are controversial with studies reporting that high oxygen concentrations during resuscitation from haemorrhagic shock are associated with significant benefits (Brod et al. 2006), while other studies report opposite effects. These reports may be germane to patients with sepsis and multi-organ dysfunction which is associated with high oxidative stress (Alonso de Vega et al. 2000, 2002; Motoyama et al. 2003).

However, the findings are difficult to reconcile. In a model of porcine faecal peritonitis, ventilation with 100 % oxygen (PEEP of 12–15 cm H₂O, tidal volumes of 8 ml/kg, long inspiratory

times) was associated with improved splanchnic and renal blood flow together with improved organ function and reduced apoptosis in both the liver and lung when instituted either at the time of early peritonitis (Barth et al. 2008) or after established shock (Hauser et al. 2009).

Thus it would appear that in the early phases of resuscitation and ventilation for sepsis, the benefits of high inspired oxygen concentrations may outweigh its side effects. However once resuscitation is well underway, the benefits of high FiO_2 may be outweighed by increased lung damage and potentiation of inflammation throughout the body.

54.5.1.2 Carbon Dioxide

Permissive hypercapnia has been well recognized as a reasonable approach to lung protection in severe lung disease (Sevransky et al. 2004) and has been associated with improved outcomes in preterm neonates with respiratory failure (Mariani et al. 1999). In addition there is evidence that the acidosis related to hypercapnia may have lung protective effects (Laffey et al. 2000, 2004b). More recently hypercarbic acidosis has been shown to have protective effects on the lung in experimental sepsis (Laffey et al. 2004a; Ni Chonghaile et al. 2008; Chonghaile et al. 2008) and also other organs (Costello et al. 2009).

Therefore, in respiratory failure due to sepsis, lung protective strategies such as permissive hypercapnia may need to be balanced against the possible deleterious effects due to pathology in other organs (e.g. the brain in meningitis) (Tasker and Peters 1998).

Although permissive hypercapnia has been accepted, there is little evidence published defining either upper levels of acceptable pCO_2 or limits of pH (Sevransky et al. 2004).

54.6 Optimization of Cardiovascular Function

Haemodynamic instability is a common feature of severe sepsis in children (Goldstein et al. 2005). While adults are likely to have normal to high cardiac output with low systemic vascular resistance in septic shock, children are more

likely to have low cardiac output with high systemic vascular resistance (Ceneviva et al. 1998; Carcillo et al. 2002). The impact of mechanical ventilation on haemodynamics depends on the interaction of many factors (Luecke and Pelosi 2005) including lung and chest wall mechanics (O'Quin et al. 1985) and characteristics of ventricular function (whether there is right, left or bi-ventricular failure) (Bronicki and Anas 2009). Cardiopulmonary interactions are generally complex (Bronicki and Anas 2009), more so in the critically ill (Pinsky 1985, 1990, 1994, 1997, 2005, 2007; Jellinek et al. 2000), and may be affected by a wide variety of issues in sepsis.

Ventilation may alter venous return in patient with sepsis. For instance, in sepsis cardiac output may be decreased because of venodilatation and reduced venous return as well as high right atrial pressures due to positive pressure ventilation (Bronicki and Anas 2009). The relationship between ventilator pressures and right atrial pressure depends on the interaction between respiratory efforts and ventilator pressures, lung resistance and compliance, chest and abdominal wall compliance and the characteristics of the pericardium and cardiac muscle (Kingma et al. 1987). Generally lung compliance in children is relatively low, while chest wall compliance is high, with the result that ventilator pressures are poorly transmitted to the right atrium. This may however not be true in sepsis, where the chest wall may become very non-compliant as a result of oedema, inflammation and raised intra-abdominal pressure.

Ventilation may also affect both right and left ventricular outputs. Right ventricular output varies depending on pulmonary vascular tone and resistance which is highest at low and high lung volumes and lowest at functional residual capacity (Bronicki and Anas 2009; Jardin 1997; Jardin and Vieillard-Baron 2003). Thus positive pressure ventilation in sepsis may reduce pulmonary vascular resistance (and impedance) and improve right ventricular function by optimizing FiO_2 , pH and lung volumes. However, over-distension of the alveoli may be associated with deterioration of right ventricular function.

Left ventricular afterload is also increased if negative intrathoracic pressures are generated

during respiration (Bronicki and Anas 2009), and thus positive pressure ventilation may substantially reduce left ventricular afterload of patients in respiratory distress who have been generating very low intrathoracic pressures (as may be seen in sepsis). This may in turn improve cardiac output.

However, the left and right ventricles do not function in isolation and ventricular interactions that may determine the effect of ventilation on cardiac output (Tyberg et al. 2000; Biondi et al. 1988).

For instance, if respiratory distress and suboptimal cardiac output coexist, the respiratory muscles may consume a significant proportion of cardiac output. Mechanical ventilation may thus contribute significantly to an improvement in organ perfusion by reducing respiratory muscle activity (Aubier et al. 1981; Viires et al. 1983).

If left ventricular dysfunction is present in the septic patient, positive pressure ventilation may be associated with significant improvements in cardiac output (Bronicki and Anas 2009), while positive pressure ventilation may substantially reduce cardiac output if the patient is hypovolaemic.

In patients with acute lung injury recruitment, manoeuvres have been used in an attempt to improve respiratory function. These manoeuvres have been associated with significant decreases in cardiac output in both animal and human adult studies (Lim et al. 2004; Toth et al. 2007).

Cardiac function in severe sepsis can therefore be profoundly affected adversely or positively by positive pressure ventilation. The exact effects will depend on the specific situation and may have to be established by careful consideration of the physiological state and sometimes a process of trial and error.

54.7 Minimizing Damage to the Lungs

The optimal ventilatory pattern to minimize damage to the lungs will depend both on the disease and on the specific lung pathology.

Although the interplay is complex, the presence of predisposing factors (such as haemorrhagic shock) may exacerbate lung injury from

inadequate ventilation (Bouadma et al. 2007), while inadequate ventilation may also exacerbate the inflammatory response to shock.

The presence of infection (or inflammation) also increases the lung and global inflammatory response to ventilation with high tidal volumes and low PEEP.

Nahum et al. (1997) demonstrated in a dog model that injurious patterns of ventilation (low PEEP and high tidal volume) significantly increased the translocation of bacteria from the lung into the circulation and the inflammatory responses within the lung.

Altemeier et al. showed in rabbits that ventilation with 10 ml/kg tidal volume had a synergistic effect, increasing lung injury, with the systemic administration of LPS (Altemeier et al. 2004). Bregeon et al. using a rabbit model showed that when *E. coli* lipopolysaccharide was administered intravenously, ventilation with zero PEEP and 10 ml/kg of tidal volume was associated with significant deterioration in lung mechanics, hypoxaemia and histological damage. Both authors demonstrated that mechanical ventilation alone did not induce lung injury, but mechanical ventilation together with aspiration of LPS was associated with an augmented inflammatory response and the development of ARDS changes (Altemeier et al. 2005).

Similar findings have been reported by others (Dhanireddy et al. 2006; O'Mahony et al. 2006; Bem et al. 2009) using a variety of models of ventilation during sepsis.

Thus a consistent theme in much experimental work in sepsis, mechanical ventilation (particularly with tidal volumes of 10 ml/kg or more) and high FiO₂ is associated with exacerbation of inflammatory responses both in the lung and throughout the body. There is little experimental data available on children, but it would seem reasonable to use "lung protective" strategies of ventilation in the setting of sepsis. There may also be a place for cautious use of "recruitment" followed by reduced pressure ventilation to minimize lung damage (Rimensberger et al. 1999).

Another consideration is the very common presence of fever in patients with sepsis. In an experimental study of ventilator-induced lung injury in rabbits, Suzuki et al. (2004)

demonstrated that lung damage using potentially injurious forms of ventilation was exacerbated by hyperthermia relative to hypothermia.

54.7.1 Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

Severe sepsis is the most common cause of both ALI and ARDS in a population-based study of ALI and ARDS in the USA (Zimmerman et al. 2009). Pneumonia and sepsis were described as the main causes of ARDS in children in study from China (Yu et al. 2009).

ARDS/ALI has also been described in patients with malaria (less frequently in children) (Taylor et al. 2006; Mohan et al. 2008), dengue (Lum et al. 1995), *Aspergillus* (Anaissie 2008), tuberculosis and a whole host of viral infections.

Many studies have highlighted the potential benefits of ventilation with lower tidal volumes in adults with ARDS (Amato et al. 1995, 1998; The Acute Respiratory Distress Syndrome Network 2000; Meade et al. 2008; Brochard et al. 1998). Although there are fewer studies in the paediatric literature, the overwhelming weight of evidence is that paediatric mortality with ARDS has decreased substantially with lower tidal volume ventilation (Hanson and Flori 2006; Mehta and Arnold 2004; Albuali et al. 2007), higher PEEP levels and permissive hypercapnia. The importance of careful attention to ventilation is highlighted in a study of children in septic shock in which hand ventilation for greater than 6 h doubled mortality (Santhanam et al. 2008).

54.7.2 Respiratory Syncytial Virus Infection

The specific effect of various modes of ventilation depends on the underlying lung pathology (Naik et al. 1998). Greenough (2009) has recently reported a wide spectrum of lung disease in RSV infection ranging from obstructive lung disease with air trapping through restrictive lung disease

with pneumonitis (Table 54.4). In response ventilatory support from CPAP through ECMO may be required in these children.

54.7.3 Tuberculosis

Tuberculosis may be responsible for a range of lung pathology in acute infection including ARDS (Agarwal et al. 2005a, b; Malhotra et al. 2005), expansile pneumonia (Goussard et al. 2004) and pneumonia (Goussard et al. 2008a), bronchopleural and broncho-oesophageal fistulae (Goussard et al. 2008b, 2007; Gie et al. 1998), laryngeal tuberculosis (du Plessis and Hussey 1987) and phrenic nerve damage related to mediastinal adenopathy (Goussard et al. 2009). Good outcomes can be achieved in children less than 6 months of age requiring ventilation for tuberculosis, but early diagnosis and therapy are essential (Goussard et al. 2008a).

A particular concern when ventilating children with tuberculosis is safety of staff and the need to identify family members with infectious tuberculosis as a potential source of nosocomial infection (Heyns et al. 2006; Schaaf et al. 2003).

54.7.4 Pertussis

Pertussis as a cause of severe pneumonia requiring intubation and ventilation has been underdiagnosed in some settings (Greenberg et al. 2007). The lung pathology in fatal cases reveals severe pulmonary hypertension and high white cell counts both of which may limit blood flow to the lung and poses significant challenges with ventilation (Table 54.3) (Paddock et al. 2008).

54.7.5 Pathologies with Limited Chest Wall Compliance

There are many potential reasons for reduction in chest wall compliance in patients with sepsis (Table 54.4). The decreased chest wall compliance may result increased pressures seen during

Table 54.3 Ventilatory concerns related to sepsis and organ failure

Lungs	Changes in lung characteristics related to infective process in the lungs Changes in lung characteristics related to generalized inflammatory process with leakage of fluid, cytokines and cells from the intravascular space Pulmonary oedema related to fluid resuscitation and/or capillary leak syndromes Interference with lung perfusion Transfusion-related lung injury	Depending on the specific pathogen, there may be significant changes in airway resistance (bronchiolitis), in lung compliance (ARDS, pneumonia) Marked leucocyte invasion seen in pulmonary vasculature in pertussis (Paddock et al. 2008)
Pleural space	Development of parapneumonic effusions and empyema Development of pneumothoraces and bronchopleural fistulae	
Chest wall	Thickening and changes of chest wall characteristics related to the fluid shifts and inflammatory processes in sepsis Changes in muscle function and particularly in diaphragmatic function related to the inflammatory processes	
Abdomen	Abdominal distension with raised intra-abdominal pressure Organomegaly related to processes such as acute or even chronic hepatic failure	
Cardiovascular concerns	Deterioration in cardiac muscle function related to inflammatory process Development of large intrathoracic pressure changes related to acidosis and increased respiratory effort. This may significantly increase cardiac afterload Fluid overload related to fluid resuscitation attempts	
Renal concerns	Renal dysfunction is common in sepsis and may be associated with acidosis, electrolyte abnormalities and fluid overload. All of these may have adverse effects on the lungs	
Hepatic concerns	Large liver (and ascites) may compromise diaphragmatic function In the setting of chronic hepatic failure, there may be an increase in intrapulmonary shunting with associated hypoxaemia	
Musculoskeletal concerns	Muscle weakness related to sepsis, organ failure or therapy	

ventilation even with modest tidal volumes, but may also limit the chances of lung damage.

Complications in the pleural space such as pneumothorax and other air leaks seen with a number of organisms including *Pneumocystis jirovecii*, *Staphylococcus aureus* and *Streptococcus pneumoniae* (Sivit et al. 1995; Wong et al. 2000) may also decrease overall compliance and may pose challenges in ventilation.

Similarly, infections with organisms such as *Staphylococcus aureus* and *Streptococcus pneumoniae* have a higher incidence of empyema which may also decrease compliance of the chest (Li and Tancredi 2009; Soares et al. 2009; Langley et al. 2008). Effective drainage of fluid, air and pus collections is essential to effective ventilation and management of these children.

Table 54.4 Pathology within the lung in the setting of sepsis

Pathology	Sepsis context
Normal lungs	Patients with meningitis
Normal lung volumes with fluid extravasation into the lung	Pulmonary oedema related to fluid administration, renal failure with failure of fluid excretion, cardiac dysfunction with backward fluid pressure, leaky capillaries related to septic damage to the lung, etc.
Diffuse inflammation with low compliance and generalized atelectasis	ARDS
Patchy changes with areas of hyperinflation and areas of collapse	Bronchopneumonia
Diffuse inflammation with air trapping	Bronchiolitis
Coagulopathy-related problems with areas of diffuse haemorrhage	
Transfusion-related lung injury	

54.8 Infection Control Issues

Mechanical ventilation of infected patients poses a risk to staff and other patients. Effective antibiotic therapy will usually render bacterial pathogens noninfective rapidly, but there are considerable concerns with viral pathogens and organisms such as tuberculosis.

Ventilator care of infected patients may be associated with nosocomial spread of infection via a variety of methods including aerosolization of organisms and contamination of ventilators, and considerable care must be implemented to prevent this risk.

Staff caring for patients with respiratory disease are also at risk of infection, particularly during procedures such as intubation or endotracheal suctioning. The experience from epidemics such as SARS suggests that health-care workers in the intensive care environment need substantial training in the use of self-protective strategies (Chia et al. 2005), while organizations need to consider the processes for staff protection (Moore et al. 2005), and ongoing research is required to assess the risk related to aerosolization of organisms and related issues (Yassi et al. 2005).

A particular concern is patients with immune deficiencies who may continue to shed pathogens a long time after the initial presentation (Arbiza et al. 2006).

54.9 Airway Humidification and Clearance in Sepsis

It is generally accepted that sputum characteristics are altered in patients with infection. Children are particularly at risk of airway obstruction from secretions as a result of the relatively small endotracheal airway utilized during endotracheal intubation and ventilation. Particular attention needs to be paid to the issues of adequate airway humidification during ventilation although the literature on this topic is extremely limited (Branson 2007; Niel-Weise et al. 2007; Ricard et al. 2006).

Suctioning is required to maintain patency of endotracheal tubes but may be associated with many and varied adverse effects (Morrow and Argent 2008). The recommendations for suctioning were recently reviewed (Morrow and Argent 2008) and include the following: no routine suctioning (except perhaps in patients on neuromuscular blockade), use appropriate size suction catheters (2X the internal diameter of the endotracheal tube (mm) will give the approximate size (FG) of the suction catheter to be used), use the minimum suction pressure required to remove secretions (with a maximum of 360 mmHg), do not use saline routinely, and limit the duration of any particular suctioning manoeuvre.

Conclusions

Sepsis in children is associated with a wide range of clinical syndromes and challenges. Appropriate ventilation in patients with sepsis requires a broad understanding of the effects of ventilation on the cardiovascular and respiratory systems, as well as local and global inflammatory responses.

In addition, it is extremely important to ensure that nosocomial spread of infection is limited and that staff are protected from the possibility of acquiring infections from their patients.

Essentials to Remember

- Sepsis may be associated with a wide variety of problems in multiple organs.
- Aims of ventilatory support will be related to the particular organs that are affected by sepsis.
- Ventilatory support must be focused on providing appropriate blood gases for the particular patient context while causing the least possible damage to the lungs.
- The effects of ventilatory support on the cardiovascular system are closely related to the specific pathophysiology in a particular patient. Cardiovascular responses to ventilation must be carefully monitored with appropriate adjustment of ventilation.
- Infection control measures, to protect both the ventilated patient and the staff and other patients, are an essential component of ventilatory support.
- Patients with sepsis may need special attention to the adequate clearance of secretions on ventilation, but this must be done with great care.

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Part XX

Mechanical Ventilation in Neuromuscular Disorders

Brigitte Fauroux

Educational Aims

- Respiratory muscles are rarely spared in neuromuscular diseases. Patients with neuromuscular disease are thus at risk of nocturnal hypoventilation and episodes of respiratory failure because of the weakness of the respiratory muscles.
- Patients with neuromuscular disease should be screened regularly for respiratory muscles weakness, and a sleep study should be performed in case of recurrent or severe chest infections and/or symptoms of sleep-disordered breathing. However, precise validated criteria for these investigations are lacking.
- Noninvasive positive pressure ventilation (NPPV), which aim is to assist or replace the respiratory muscles, corrects

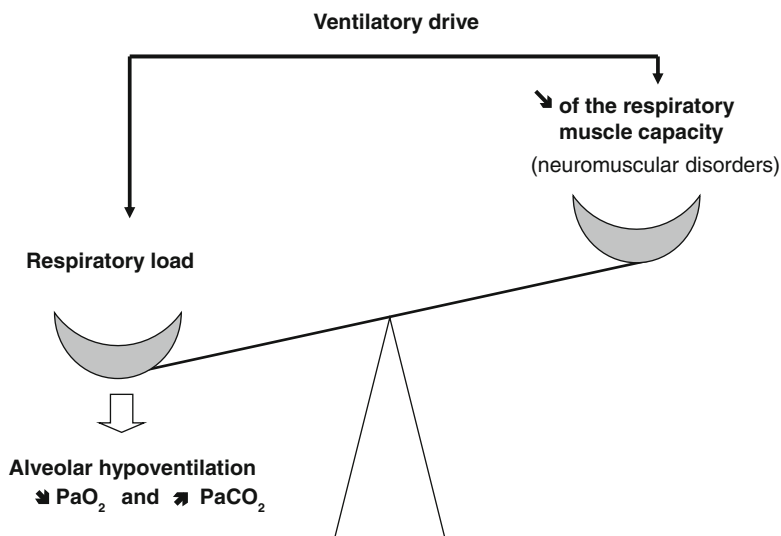
alveolar hypoventilation. NPPV is preferentially used at night but can be extended during daytime when respiratory muscle weakness progresses.

- Cough-assisted techniques are recommended in case of recurrent chest infections and respiratory muscle weakness sufficiently severe to require NPPV.

Respiratory muscles are rarely spared in neuromuscular diseases, although the importance and evolution of the respiratory muscle involvement vary according to the type of neuromuscular disease. Weakness of the respiratory muscles causes alveolar hypoventilation, which predominates during sleep, and may lead to respiratory failure, which is commonly precipitated by a chest infection. Noninvasive positive pressure ventilation (NPPV), by assisting or replacing the respiratory muscles, restores a normal alveolar ventilation and gas exchange. NPPV is preferentially used at night, during sleep, but can be extended during daytime when respiratory muscle weakness progresses. Monitoring of lung function, respiratory muscle performance and sleep is essential to determine the optimal timing of NPPV. After the initiation of NPPV, regular monitoring of nocturnal gas exchange is mandatory.

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Fig. 55.1 The ability to sustain spontaneous ventilation can be viewed as a balance between neurological mechanisms controlling ventilation together with ventilatory muscle power on one side and the respiratory load, determined by lung, thoracic and airway mechanics, on the other. Weakness of the respiratory muscles, as observed in patients with neuromuscular disease, causes a respiratory imbalance, responsible for alveolar hypoventilation. PaO_2 partial arterial oxygen pressure, $PaCO_2$ partial arterial carbon dioxide pressure



55.1 Introduction

Neuromuscular diseases (NMD) represent a heterogeneous group of disorders of the muscle, nerve or neuromuscular junction. The weakness of the peripheral muscles is responsible for the clinically evident physical limitation, which contrasts with the often more subtle weakness of the respiratory muscles. However, the decrease of strength and endurance of the respiratory muscles is responsible for the greatest morbidity and mortality in patients with NMD. Indeed, the respiratory muscles are rarely spared in NMD, even if the severity and course of the respiratory muscle weakness vary among the different diseases. Weakness of the respiratory muscles may be responsible for alveolar hypoventilation. Indeed, when the load imposed on the respiratory system exceeds the capacity of the respiratory muscles, the patient may develop alveolar hypoventilation, in particular during respiratory tract infection, because of the insufficient respiratory muscle reserve, and during sleep, which is a situation associated with a physiological degree of alveolar hypoventilation. Regular monitoring of the patient's lung and respiratory muscle function is thus recommended to detect when a patient may be at risk to develop respiratory failure triggered by a chest infection, and nocturnal hypoventilation, in order to initiate cough-assisted techniques and noninvasive positive pressure ventilation (NPPV).

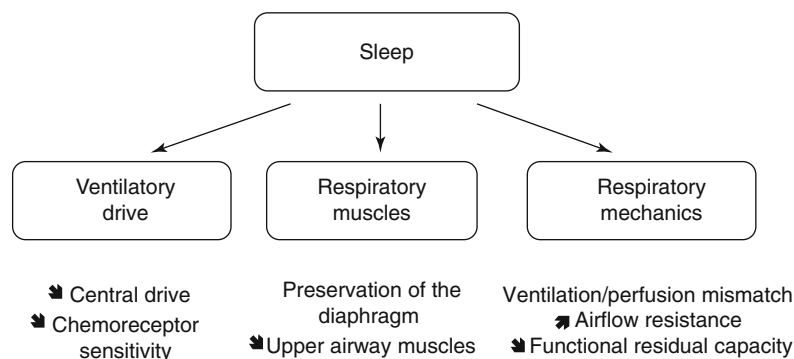
This chapter will give an overview of the pathophysiology of respiratory failure in patients with NMD, the benefits and expectations of NPPV, the usefulness of other respiratory techniques such as cough-assisted techniques and the practical implementation and monitoring of NPPV.

55.2 Pathophysiology of Respiratory Failure in Patients with NMD

55.2.1 Weakness of the Respiratory Muscles

The ability to sustain spontaneous ventilation can be viewed as a balance between neurological mechanisms controlling ventilation together with ventilatory muscle power on one side, and the respiratory load, determined by lung, thoracic and airway mechanics, on the other (Fig. 55.1). Significant dysfunction of any of these components of the respiratory balance may impair the ability to spontaneously generate efficacious breaths. In healthy individuals, central respiratory drive and ventilatory muscle power exceed respiratory load; they are thus able to sustain adequate spontaneous ventilation. However, if the respiratory load is too high and/or ventilatory muscle power or central respiratory drive is too

Fig. 55.2 Sleep is associated with a physiological degree of alveolar hypoventilation because of changes in respiratory mechanics, respiratory and upper airway muscles and respiratory drive



low or inadequate, ventilation may be insufficient, resulting in hypercapnia and hypoxemia.

The weakness of the respiratory muscles is the main contributor of the imbalance of the respiratory balance in patients with NMD. In patients with Duchenne muscular dystrophy (DMD), the weakness predominates on the diaphragm and the expiratory muscles and progresses ineluctably with age (Nicot et al. 2006). The spinal muscular atrophies (SMAs) are inherited autosomal recessive disorders. Severity is inversely proportional to the amount of survival motoneuron protein in the anterior horn cell. SMAs range from essentially total paralysis and need for ventilatory support from birth to the relatively mild muscle weakness presenting in the young adult. Diaphragmatic strength is generally preserved, and respiratory muscle weakness predominates on the other inspiratory muscles and the expiratory muscles (Nicot et al. 2006). Respiratory failure is less frequent in other muscular dystrophies, such as Becker, limb-girdle and facioscapulo-humeral dystrophies. Patients with congenital myopathies represent a heterogeneous group of patients, with a various involvement of the respiratory muscles (Nicot et al. 2006). However, the respiratory condition of these children may deteriorate functionally with growth because weakened muscles are unable to cope with increasing body mass and energy demand.

Patients with NMD have normal lungs, airways and chest wall. Respiratory load is thus expected to be within the normal range. However, measurements of the oesophageal (PTPoes) and diaphragmatic pressure time product (PTPdi), which are correlated to the oxygen consumption

of the global inspiratory muscles for PTPoes, and of the diaphragm for PTPdi, have shown values 2–3 times higher than normal (Nicot et al. 2006). This apparently abnormal increase in respiratory load may be explained by the chronic limitation of the respiratory movements, leading to progressive “micro-atelectasis” and stiffening of the rib cage. Weakness of the paravertebral muscles may promote thoracic deformity, such as scoliosis, which may also increase respiratory load. However, central drive is normal, and even increased in case of significant respiratory muscle weakness, as reflected by the increase in the pressure swing occurring 100 ms after the onset of the inspiration (P0.1) (Fauroux et al. 2009; Mulreany et al. 2003). Also, the ventilatory response to carbon dioxide (CO₂), which is a strong respiratory stimulant, is directly correlated to the strength and the endurance of the respiratory muscles in patients with NMD (Fauroux et al. 2009; Toussaint et al. 2007).

55.2.2 Consequences of the Weakness of the Respiratory Muscles

Ventilation has to adapt to various physiological and pathological situations. Physiological situations are represented by sleep and exercise. Sleep is associated with changes in respiratory mechanics, such as an increase in ventilation-perfusion mismatch, an increase in airflow resistance and a fall in functional residual capacity (Fig. 55.2). Although the activity of the diaphragm is preserved, that of the intercostal and the upper

airway muscles is decreased significantly. The physiological relaxation of the upper airway muscles contributes to a certain degree of upper airway obstruction that may aggravate the fall in alveolar ventilation. Finally, central drive and chemoreceptor sensitivity are less efficient during sleep than during wakefulness. All these abnormalities explain a physiological degree of nocturnal hypoventilation in healthy subjects, causing a rise in partial arterial carbon dioxide pressure (PaCO_2) of up 3 mmHg (0.4 kPa). This decrease in alveolar ventilation predominates during rapid eye movement (REM) sleep.

A correlation between respiratory muscle strength, represented by a global marker of respiratory muscle strength, i.e. vital capacity, and sleep-disordered breathing has been observed in patients with NMD (Ragette et al. 2002). Indeed, as the fall of inspiratory vital capacity progresses, hypoxia appears during REM sleep, total sleep time and daytime. The detection of nocturnal hypoventilation is thus mandatory after the occurrence of a certain degree of respiratory muscle weakness, which depends on the type of NMD. Markers associated with the occurrence of nocturnal hypercapnia have been identified for patients with DMD. Indeed, vital capacity and rapid shallow breathing have been shown to be sensitive predictors for daytime hypercapnia (Toussaint et al. 2007). However, predictors for nocturnal hypoventilation have not been clearly identified for other NMD.

Respiratory tract infection represents the most common situation that may precipitate respiratory failure in patients with NMD. Respiratory failure develops when tidal volume decreases, the patient being unable to generate a sufficiently negative intrathoracic pressure due to the weakness of his respiratory muscles. Metabolic demands are increased during a respiratory tract infection, and caloric intake is generally insufficient, leading to weight loss and malnutrition, which aggravate respiratory muscle weakness. Recurrent or prolonged chest infections are the signature of an insufficient respiratory muscle reserve and justify a respiratory muscle investigation and the implementation of cough-assisted techniques and eventually NPPV. Indeed, children with NMD having

a history of recurrent chest infection had significantly lower inspiratory vital capacity, forced expiratory volume in 1 s (FEV1) and peak cough flow than those without a history of recurrent chest infections (Dohna-Schwake et al. 2006).

55.3 Benefits of NPPV in Patients with NMD

The role of NPPV is to assist or replace the patient's respiratory muscles in order to normalise alveolar ventilation. Nocturnal NPPV is associated with a correction of gas exchange during sleep (Annane et al. 2007). Most interestingly, regular intermittent use of NPPV may correct gas exchange during spontaneous breathing (Mellies et al. 2003). This residual effect of NPPV may be explained by the resetting of ventilatory drive in case of chronic hypercapnia, the rest of the respiratory muscles and the increase of chest wall and lung compliance due to NPPV (Nickol et al. 2005). However, NPPV has not been shown to improve symptoms related to sleep-disordered breathing (Annane et al. 2007). Neither has any study shown that NPPV is associated with an improvement or a stabilisation of lung or respiratory muscle function (Annane et al. 2007).

By assisting the respiratory muscles, NPPV is expected to prolong survival. This major beneficial effect has been observed for patients with DMD and SMA type I. Indeed, data from the national Danish DMD registry over a period of 30 years observed an association between the decrease in mortality rate and the increase in NPPV use (Jeppesen et al. 2003). Also, survival of children with SMA type I increased over the period 1995–2006 as compared to the period 1980–1994, due to the combined use of mechanical ventilation, cough-assisted techniques and nutritional support by means of a gastrostomy (Oskoui et al. 2007).

Quality of life is a major issue for patients with chronic diseases who are proposed lifelong technological support such as NPPV. Several studies in children and adults have shown that the implementation of NPPV is not associated with a decrease in quality of life, except for the physical

components, which reflect the progression of the peripheral muscle weakness (Kohler et al. 2005; Raphael et al. 2002; Young et al. 2007). Indeed, all social and emotional components remained stable after the start of NPPV. Most importantly, patients usually score their quality of life better than do their parents, grandparents or health care givers (Bach et al. 2003; Young et al. 2007).

Sufficient respiratory movements are necessary for normal lung and chest wall growth and even lung differentiation in the antenatal period. Abnormal development of the diaphragm and the intercostal muscles leads to lung hypoplasia in mice (Inanlou and Kablar 2003, 2005). In clinical practice, hypoplasia and deformation of the chest, and consequently of the lung, may be observed in infants and young children in whom the consequences of respiratory muscle weakness are the most pronounced (Bach and Bianchi 2003). The ability of NPPV to preserve normal lung and chest wall growth is thus an important question, which remains unresolved.

55.4 When to Start NPPV in Patients with NMD

All experts agree on the necessity to start NPPV in patients with NMD who have daytime hypercapnia or a history of a severe respiratory exacerbation (A Consensus Conference Report 1999; ATS Consensus Conference 2004; Robert et al. 1993). Indeed, these two situations are the signature of overt respiratory failure, the patient being unable to maintain sufficient minimal alveolar ventilation while awake in the first situation and having insufficient respiratory muscle reserve in the second case. As stated before, the regular use of nocturnal NPPV is associated with a normalisation of nocturnal and daytime gas exchange (Annane et al. 2007). However, the objective benefit of NPPV to reduce the hospitalisation rate is less clear (Annane et al. 2007).

In patients with NMD, alveolar hypoventilation develops insidiously, over periods of months or years. The two classical criteria are preceded by a variable period of nocturnal hypoventilation during which treatable symptoms, such as frequent

arousals, severe orthopnea, daytime fatigue and alterations in cognitive function, may deteriorate the daily life of the patient. This situation represents clearly a risk situation as observed in a recent study in which only one out of ten patients with isolated nocturnal hypercapnia did not require NPPV for daytime hypercapnia or respiratory failure over a 24-month period (Ward et al. 2005). The effect of NPPV on sleep quality and especially arousals and sleep fragmentation has been poorly studied. Sleep-disordered breathing is associated with neurocognitive dysfunction in children, and it is possible that the use of NPPV may be associated with an improvement in memory, attention and mood in children with NMD and nocturnal hypoventilation. A major challenge is thus to determine the optimal timing for a sleep study in a paucisymptomatic patient (Fauroux and Lofaso 2005). A polysomnography should be realised without delay when the patient recognises symptoms related to sleep-disordered breathing, but patients with NMD tend to underestimate symptoms such as fatigue before using mechanical ventilation. Sleep-disordered breathing is difficult to establish in children because of reliance on parents and second-hand caregivers who have a different perception of the child's disease. Future studies should thus try to determine the most pertinent criteria to schedule a sleep study, according to the type of NMD. But then, the difficulty remains concerning the definition of nocturnal hypoventilation. Most often, this definition is based on a cut-off PCO_2 value, which is transgressed during a defined percentage of sleep time or of study period. But other respiratory events during sleep, as those recently recommended for the diagnosis of sleep-related breathing disorders, such as sleep fragmentation, may be important to be taken in account. Moreover, it may be possible that the optimal definition of nocturnal hypoventilation differs according to the underlying disease and also in children compared to adults. A definition exclusively based on the PCO_2 value may be too restrictive and insufficiently relevant from a clinical perspective.

The weaning from invasive ventilation for a severe acute respiratory exacerbation by means of NPPV is also an important issue. A child with NMD on invasive ventilation may be extubated

and switched to NPPV when the following criteria are fulfilled: an inspired fraction of oxygen (FiO_2) close to room air, minimal respiratory secretions and an acceptable inspiratory and expiratory pressures on the ventilator (<20 and $6 \text{ cm H}_2\text{O}$ for the inspiratory and expiratory pressures, respectively). NPPV with cough-assisted techniques should be used intensively after extubation with similar pressure levels and backup rate. The weaning of NPPV should associate increasing periods of spontaneous breathing, separated by periods of NPPV without decreasing the pressure levels and backup rate. The occurrence of a respiratory exacerbation requiring invasive ventilation is the signature of insufficient ventilatory reserve and severe respiratory muscle weakness, justifying the long-term maintenance of NPPV in most cases.

55.5 How to Ventilate Patients with NMD

55.5.1 Ventilatory Modes

The role of NPPV in patients with NMD is to maintain a sufficient tidal volume and minute ventilation by assisting or replacing the patient's respiratory muscles. This goal can be achieved with different ventilatory modes. The first mode proposed to patients with NMD was volume-targeted ventilation. This mode is characterised by the delivery of a fixed, predetermined tidal volume. Its main advantage is that a guaranteed minimal tidal volume is delivered, but this can result in detrimentally high inspiratory airway pressures causing discomfort and poor tolerability. Another limitation is the lack of leak compensation, which is a major cause of persistent hypercapnia in patients with NMD (Gonzalez et al. 2003). However, this mode is suited for patients with neuromuscular diseases where the ventilator acts as a substitute for the weakened respiratory muscles, which are unable to trigger the ventilator. A relatively high backup rate (2–3 breaths lower than the spontaneous respiratory rate of the patient) is recommended to avoid nocturnal desaturations, and, as a consequence, many patients adopt a controlled

mode without triggering the ventilator. Also, the inspiratory triggers of these ventilators are not very sensitive, which is another factor justifying the use of a relatively high backup rate (Fauroux et al. 2008b). These volume-targeted ventilators designed for home use are relatively portable. They are not as technologically sophisticated as hospital ventilators. Furthermore, few of them are capable to operate within certain limits (i.e. tidal volume <50 – 100 ml).

Pressure support (PS) is a more recent pressure-targeted mode during which each breath is triggered and terminated by the patient and supported by the ventilator; the patient can control his respiratory rate, inspiratory duration and tidal volume (Brochard et al. 1987). This explains the relative ease in adapting to and the greater comfort and synchrony of this mode. In contrast to volume-targeted ventilation, tidal volume is not predetermined but depends on the level of PS, the inspiratory effort of the patient and the mechanical properties of the patient's respiratory system. During this mode, since there are no mandatory breaths present, an in-built low-frequency backup rate is used to prevent episodes of apnoea. Furthermore, because the breaths are triggered by the patient, the sensitivity of the trigger is crucial. The sensitivity of the inspiratory triggers of the different ventilators designed for the home is variable, but some are as sensitive as those of intensive care devices (Lofaso et al. 1996). Because during PS, inspiratory muscle activity may influence respiratory frequency and tidal volume, this ventilatory mode is generally proposed in patients who can breathe spontaneously for substantial periods of time and require mainly nocturnal ventilation. This mode can be used in patients with NMD who are able to trigger the ventilator, but as their disease progresses, there is a risk of underventilation.

Bi-level PPV is the combination of PS and PEEP, permitting an independent adjustment of expiratory positive airway pressure (EPAP) and inspiratory positive airway pressure (IPAP). In this condition upper airway obstruction and/or work of breathing induced by intrinsic positive end-expiratory pressure (PEEP) is prevented by EPAP, and thus PS can be triggered easily by the patient. This ventilatory mode has been used in children with

neuromuscular disease, but the rationale of the use of an EPAP is not validated in patients who are not supposed to have intrinsic PEEP.

The triggers and performances of most ventilators proposed for home NPPV are not optimal for children. Moreover, in case of severe respiratory muscle weakness, as in SMA type I, the patient will not be able to trigger the ventilator. A backup rate that matches the patient's breathing rate is thus recommended in most cases. Experience shows that with this approach, the patient rapidly adopts the ventilator backup rate, which improves patient-ventilator synchrony.

For all ventilatory modes, alarms must be correctly set. When positive pressure ventilators are used, low-pressure or disconnect alarms are classically present. Alarms for high pressure, incorrect timing and power failure are also frequently present. The alarm of a minimal tidal volume is useful in children. All these alarms must be carefully checked before the discharge of the patient.

The need for NPPV implies severe respiratory muscle weakness which impairs also the cough manoeuvre. A careful evaluation of the patient's ability to cough and the implementation of cough-assisted techniques are thus warranted in all patients treated with NPPV (Fauroux et al. 2008a; Nicot et al. 2006).

55.5.2 Interfaces

The necessity of interfaces specifically designed for children represents an important technical limitation of NPPV in paediatric patients. In adults, four different types of interfaces are used: full face masks (enclose mouth and nose), nasal masks, nasal pillows or plugs (insert directly into the nostrils) and mouthpieces. Nasal pillows and plugs are too large for children, and mouthpieces require a good cooperation and are difficult to use in neuromuscular patients. In young children, nasal masks are preferred because they have less static dead space, are less claustrophobic and allow communication and expectoration more easily than full face masks. Nasal masks allow also the use of a pacifier in infants, which contributes to the better acceptance of NPPV and the reduction of mouth leaks.

Face masks should not be used in patients with NMD because of the risk of inhalation in case of gastro-oesophageal reflux in patients who have a limited use of their upper limbs. Few industrial masks are available for children. This shortcoming is even more important for infants. For young children, NPPV is thus restrained to some highly specialised paediatric centres which have the possibility to manufacture custom-made masks.

55.5.3 Limitations and Side Effects of NPPV

Side effects of NPPV are common. They are caused by the interface and the delivery of a positive pressure. Skin injury, from transient erythema to permanent skin necrosis, due to the nasal mask, has been observed in 53 % of the 40 patients during their routine 6-month follow-up in our department (Fauroux et al. 2005). In young children, there is also a potential risk of facial deformity, such as facial flattening and maxilla retrusion, caused by the pressure applied by the mask on growing facial structures. These potential side effects justify the systematic evaluation before the initiation and during the follow-up of children receiving NPPV by a paediatric maxillofacial specialist. Abdominal distension is an uncommon problem which can be resolved by switching to a PS ventilator or decreasing the tidal volume on a volume-targeted ventilator (Guilleminault et al. 1995).

NPPV is not always successful in adequately relieving hypoventilation. Regular monitoring of nocturnal gas exchange, and in particular CO₂, is mandatory for all patients receiving long-term NPPV. Indeed, persistent asymptomatic hypercapnia is common and is frequently caused by air leaks (Gonzalez et al. 2003; Paiva et al. 2009). Simple practical measures such as changing the mask, using a chin strap, increasing minute ventilation and changing the type of the ventilator are able to reduce the volume of air leaks and improve the efficacy of ventilation (Gonzalez et al. 2003; Paiva et al. 2009).

However, despite these measures, in progressive diseases such as some neuromuscular diseases, a tracheotomy may become necessary at a

Table 55.1 Contraindications for NPPV

<i>Relative contraindications</i>
Severe swallowing impairment
Inadequate family/caregiver support
Need for full-time ventilatory assistance
<i>Absolute contraindications</i>
Severe upper airway obstruction
Uncontrollable secretion retention
Inability to cooperate
Inability to achieve adequate peak cough flow, even with assistance
Inability to fit a noninvasive interface

certain moment (Table 55.1). Close monitoring of the patient's physiological status and disease progression, together with clear information of the family, is essential to discuss the possibility of a tracheostomy with the patient and his (her) family with regard to the patient's benefits and quality of life.

Future Perspectives

- Determine the optimal timing for a sleep study and the initiation of NPPV in children with NMD.
- Determine the efficacy of NPPV to preserve normal lung and chest wall growth in young children with NMD.
- Demonstrate the efficacy of NPPV to improve symptoms of sleep-disordered breathing and sleep quality.
- Evaluate the benefit of NPPV on quality of life in children with NMD and their family.

Essentials to Remember

- Children with NMD should have regular evaluation of their lung and respiratory muscle function.
- A sleep study should be performed when a patient with NMD presents with symptoms of sleep-disordered breathing, recurrent and/or severe chest infections and/or severe respiratory muscle weakness.

- Oxygen therapy is not the treatment of patients who hypoventilate such as patients with NMD. Hypoventilation can only be reversed by mechanical ventilation, which is preferentially administered noninvasively.
- Patients should be regularly and closely monitored after NPPV initiation, to ensure a perfect correction of alveolar hypoventilation and to detect side effects of NPPV, such as skin injury or facial deformity.

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Part XXI

Specific Conditions

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Educational Goals

- Review the technical considerations and indications for tracheostomy in the pediatric ICU
- Review clinical practice and experience with a focus on tips to improve the assessment and care of the patient being mechanically ventilated with a tracheostomy tube
- Discuss considerations and pitfalls when ventilating a patient with a tracheostomy tube

Pediatric tracheostomies provide life-sustaining artificial airway support to patients with acute or chronic airway obstruction, neurologic impairment such as disordered control of breathing or severe neuromuscular weakness, or chronic conditions with inadequate spontaneous gas exchange

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during breathing. In addition to overcoming anatomic and physiologic obstacles to ventilation, tracheotomies can also provide nutritional, developmental, and social benefits.

Tracheostomies can be intimidating for families and healthcare providers, but with proper instruction, support, and experience, they can develop the comfort and skills necessary to successfully manage and troubleshoot tracheotomies during both routine and emergency care. In this chapter, we will review the technical considerations, indications, clinical practice tips, and specific considerations for ventilating a patient with a tracheostomy.

56.1 Technical Considerations

The term tracheostomy describes a stoma, or an opening, through the neck into the trachea, below the vocal folds (commonly referred to as vocal cords), which provides a physical pathway for ventilation. A tracheotomy tube is the artificial airway that is inserted into this opening, to provide stability and access. Depending on the pulmonary support requirements of the patient, the tracheotomy tube may be connected to a ventilator to provide respiratory support, or it could be covered with a simple filter which functions to trap exhaled humidification while simultaneously preventing debris from entering the lungs. In either circumstance, air flowing through the tracheotomy tube bypasses the larynx and its functions, which include preventing aspiration, protecting the lower airway, regulating airflow,

and contributing to phonation (O'Connor 1995). Without compensatory maneuvers, air escape through a tracheotomy interferes with vocalization and with accomplishing effective cough or Valsalva maneuver. Similarly, airflow through a tracheotomy bypasses the nose and its function to warm, humidify, filter, and regulate airflow (Bergeson and Shaw 2001; Lane 2004). Airflow bypass of the olfactory epithelium in the roof of the nose affects the sense of smell which, in humans, contributes to the perception of taste, warns of impending hazards, and affects social interactions (Cressman and Naclario 2003).

Although adult tracheotomy tubes have inner cannulas, the smaller size of the pediatric airway, combined with the wall thickness of modern plastic pediatric tracheotomy tubes, makes an inner cannula impractical. Cleaning or changing the tracheotomy tube requires removing the entire tracheotomy tube. Modern pediatric tracheotomy tube size designation is based approximately on the diameter of the inner lumen, similar to the size designations of tracheal tubes. Some tracheotomy tube shafts contain wire reinforcement, which can interfere with radiologic imaging. Neonatal tubes have the same inner and outer diameters but shorter lengths than their pediatric counterparts. For very specialized purposes, such as during multistep laryngotracheal reconstruction, “T-tubes” and metal tracheotomy tubes with inner cannulas are available (Figs. 56.1 and 56.2).

Cuffless tubes are used for most pediatric patients with tracheostomies (Fig. 56.3), with an air leak around the tracheal tube used to preserve vocalization on exhalation. Patients with less compliant lungs often require a cuff to attain adequate inflation pressures for the lungs. Cuffs can be inflated with air or sterile water, depending on the manufacturer's recommendation. Saline should not be used to inflate cuffs because they can form crystals that clog the inflation/deflation valve. Self-expanding foam cuffs are not commonly used.

Speaking valves are devices which fit on the end of the tracheotomy and contain a soft plastic flap that allows air to flow in through the tracheotomy during inspiration but prevents air from flowing out through the tracheotomy during expiration. This forces the air to egress through the vocal folds, thereby supporting phonation,

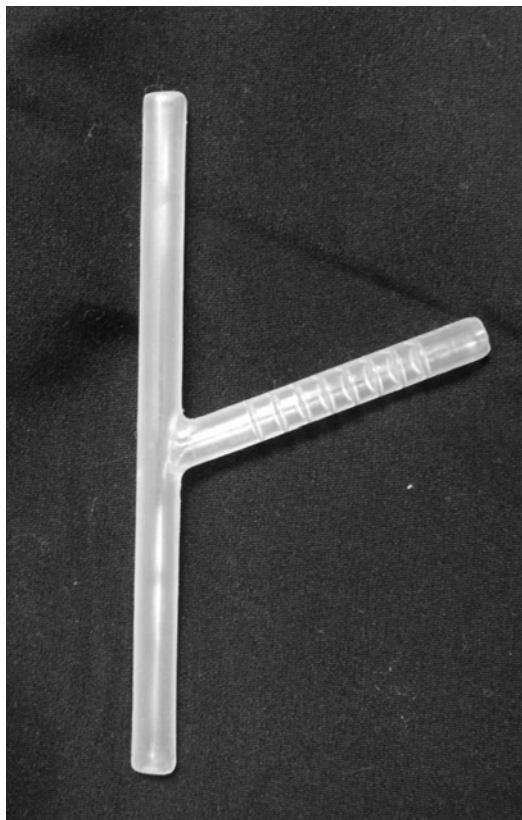


Fig. 56.1 A T-tube may be used instead of a tracheotomy tube for special circumstances, such as after surgery on the larynx or trachea



Fig. 56.2 Silver tracheotomy tube, containing an inner cannula, and an obturator for use during replacement of the tube

Fig. 56.3 The tracheotomy tube on the left contains an obturator and has extension external to the flange (*arrow*). The tracheotomy tube on the right has an inflated cuff, inflated through the port at the pilot. The middle item is the obturator for the cuffed tracheotomy tube



effective cough, and Valsalva maneuvers. Speaking valves have been used for patients as young as 13 days of age (Engleman and Turnage-Carrier 1997) and for patients who require mechanical ventilation (Hull et al. 2005). A speaking valve is contraindicated in patients with severe subglottic stenosis or other lesions that might cause air-trapping. Some patients spontaneously learn to accomplish this same objective of forcing expiration through the vocal folds, either by occluding the end of the tracheotomy tube manually or by using their chins.

Mechanical issues may also be important. The external connector to a bag-mask device or mechanical ventilator tubing is universally sized but often is rather large relative to the neck of an infant and may interfere with normal head positioning or cause pressure at the stoma. Some tracheotomy tubes incorporate an extension which increases the distance between the universal adaptor and the tracheotomy flange, allowing more normal head positioning. The connections between the tracheotomy adaptor and the ventilator tubing can loosen, leak, or disconnect, particularly while turning or repositioning a patient. Extra caution to prevent disconnection or even decannulation is indicated if the patient requires extreme head positioning or if head turning is required for access to the lateral neck (e.g., for internal jugular central venous catheter placement). Some surgeons suture the tracheotomy flange to the skin of the neck for new tracheotomies; in this case scissors or a

scalpel should be immediately available in case there is an emergency, such as a tracheotomy plug or tracheotomy displacement, requiring tracheostomy tube removal and replacement.

56.2 Indications

Pediatric tracheostomies can bypass upper and central airway obstruction and facilitate mechanical ventilation including positive end-expiratory pressure (PEEP) delivery to lower airways and facilitate eating, aerosol delivery, suctioning, and tracheobronchial toilet (Mahadevan et al. 2007; Davis 2006; Carron et al. 2000; Parrilla et al. 2007). Whether or not a tracheostomy tube can prevent pulmonary aspiration, even when the cuff is properly inflated, is controversial.

In adults, a large proportion of tracheotomies are performed to support long-term mechanical ventilation (Goldenberg et al. 2002). In contrast, many authors assert that most pediatric tracheotomies are performed to bypass various causes of upper airway obstruction (Goldenberg et al. 2002; Parrilla et al. 2007; Trachsel and Hammer 2006; Mahadevan et al. 2007; Davis 2006). Comparisons between reported series are limited by a lack of standardized system of classification.

In children, upper and central airway obstruction can be caused by a large variety of

congenital or acquired lesions, affecting any aspect of the respiratory system proximal to the trachea, from the anterior nares to the subglottis. Examples of abnormalities which interfere with breathing include conditions which affect the mouth and nose, such as Robin sequence or other craniofacial abnormalities; lesions that affect the larynx directly, such as severe laryngomalacia and vocal fold paralysis; and lesions that have variable locations in the airway, such as neoplasms like hemangiomas and lymphangiomas (Table 56.1). Airway obstruction can result from infection and from physical, chemical, or burn-induced trauma, as well as from conditions restricting lung excursion, such as campomelic dysplasia or morbid obesity.

Many conditions which interfere with ventilation in infants, such as severe tracheomalacia, are expected to improve over time. In contrast, chronic neuromuscular disease, such as muscular dystrophy, spinal muscular atrophy, or severe developmental delays which interfere with the patient's ability to breathe, swallow, cough effectively, or otherwise protect his airway, may progress over time. The majority of pediatric tracheotomies are performed in children less than 1 year of age (Mahadevan et al. 2007; Carron et al. 2000).

56.2.1 Subglottic Stenosis

Subglottic stenosis is a common indication for tracheostomy in children, although alternative management options to avoid tracheostomy may be appropriate for selected individuals. Currently, most subglottic stenosis in infants is "acquired" as a result of prolonged or traumatic tracheal intubation (Fig. 56.4). Despite the fact that younger and younger infants are surviving, and often require prolonged respiratory support, there is a trend toward a decreasing incidence of subglottic stenosis (Walner et al. 2001). Older reports of neonatal subglottic stenosis describe an incidence of 6–20 % (Parrilla et al. 2007; Mahadevan et al. 2007; Davis 2006; Carron et al. 2000). A recent systematic review reports an incidence of less than 0.63 % of all neonates in studies published after 1990, with a projected

current range of 0–2 % of intubated neonates (Walner et al. 2001).

The subglottis is contained within the only true complete cartilaginous ring in the airway; therefore, it cannot expand to accommodate distension by endotracheal tubes, and its loose areolar submucosa has the potential to become edematous when inflamed (Willing and Cotton 1995). If narrowing in the subglottis matures into a firm scar, it becomes subglottic stenosis. Normal subglottic lumen in a full-term neonate is at least 4 mm (Willing and Cotton 1995), so a subglottic lumen of less than 4 mm is considered stenotic in newborns. In larger children, abnormal narrowing proportional to the normal size of the subglottis is also considered stenosis, and the severity is commonly graded using the Myer-Cotton grading system (Myer et al. 1994). Because of its narrow diameter, even small amounts of edema, from intubation, instrumentation, or other causes, will result in large decreases in the caliber of the airway. Stenosis is considered congenital if there is no history of airway instrumentation, trauma, or infection.

Alternative management may be possible for some children in order to avoid a tracheostomy. Immediately after extubation, systemic or inhaled steroids may alleviate post-intubation subglottic edema, and heliox may be of use in optimizing ventilation while edema subsides. For patients with micrognathia, such as those with Robin sequence, distraction osteogenesis may alleviate upper airway obstruction. Patients with severe laryngomalacia may benefit from epiglottoplasty. Airway examination such as direct (rigid) laryngoscopy and bronchoscopy occasionally identifies reversible causes of airway obstruction, such as subglottic cysts, or posterior glottic synechiae.

When a tracheostomy is under consideration, discussion with the family should include information about the potential risks, benefits, and alternatives to a tracheostomy, as well as preliminary information about long-term management of a child with a tracheostomy. If the family will eventually care for their tracheotomized child in their own home, they will need anticipatory guidance and then practical support to develop the necessary skills, equipment, and nursing resources.

Table 56.1 Indications for tracheotomy, compiled from review articles by Mahadevan et al. (2007), Davis (2006), Parrilla et al. (2007), and Carron et al. (2000)

	Mahadevan et al. (New Zealand)	Patients (%)	Davis	Patients (%)	Parrilla et al. (Italy)	Patients (%)	Carron et al. (USA)	Patients (%)
Airway and air-way related	Airway obstruction	86 (70)	Unsafe or obstructed airway	36 (55)		38 (100)	Upper airway obstruction	38 (19)
	Craniofacial dysmorphism	40 (33)	Subglottic stenosis	13 (20)	Neuromuscular or respiratory problems	17 (45)	Subglottic stenosis	13 (6)
	Subglottic stenosis	18 (15)	Subglottic hemangioma	4 (6)	Congenital malformations (4 laryngotracheal anomaly, 3 cardiovascular anomaly, 1 pulmonary anomaly)	8 (21)	Tracheomalacia	8 (4)
	CNS	6 (5)	Vocal cord palsy	4 (6)	Craniofacial syndromes/Obstructive sleep apnea syndromes	6 (16)	Pharyngeal stenosis	2 (1)
	Vocal cord palsy	6 (5)	Other (craniofacial syndromes, glossoptosis, pharyngeal, hypotonia, epiglottitis)	15 (23)	Acquired subglottic stenosis	5 (13)	Subglottic hemangioma	2 (1)
	Hemangioma	5 (4)			Tracheoesophageal burn	1 (3)	Tracheal stenosis	2 (1)
	Laryngomalacia	4 (3)			Trauma	1 (3)	Other	11 (5)
	Cavernous lymphangioma	4 (3)					Craniofacial syndromes	27 (13)
	Other	3 (2)					Pierre-Robin sequence	5 (2)
							Treacher Collins disease	5 (2)
							Beckwith-Wiedemann syndrome	3 (1)
							Nager syndrome	2 (1)
							Other	5 (2)
							Trauma	15 (7)
							Closed head injury	12 (6)
							Laryngeal fracture	1 (<1)
							Laryngeal or tracheal injury	1 (<1)
							Cervical spine fracture	1 (<1)
							Vocal fold paralysis	15 (7)
							Hydrocephalus	3 (1)
							Sandhoff disease	1 (<1)
							Leukodystrophy	1 (<1)
							Neurofibromatosis	1 (<1)
							Mobius syndrome	1 (<1)
							Idiopathic or unspecified	7 (3)

(continued)

Table 56.1 (continued)

	Mahadevan et al. (New Zealand)	Patients (%)	Davis	Patients (%)	Parrilla et al. (Italy)	Patients (%)	Carron et al. (USA)	Patients (%)
Prolonged ventilation	Prolonged ventilation	36 (30)	Mechanical ventilation	15 (23)			Prolonged intubation	53 (26)
	Trauma	9 (7)	Central nervous system abnormality	5 (8)			Prematurity or BPD	37 (18)
	Postoperative	9 (7)	Cyanotic heart disease	4 (6)			Congenital heart disease	3 (1)
	Infection	8 (7)	Respiratory failure	4 (6)			Pneumonia	2 (1)
	Neurological	4 (3)	Respiratory infection	1 (2)			Other	11 (5)
Tracheobronchial toilet	Bronchopulmonary dysplasia	3 (2)	Sepsis	1 (2)				
	Online's curse	3 (2)						
			Tracheobronchial toilet, aspiration risk	14 (22)			Neurologic impairment	56 (27)
			Trauma-related head injury	10 (15)			Cerebral palsy	18 (9)
			Hypoxic brain injury	2 (3)			Hypoxic encephalopathy	4 (2)
			Intracerebral hemorrhage	1 (2)			Werdnig-Hoffmann syndrome	4 (2)
			Respiratory infection	1 (2)			Spina bifida	3 (1)
							Myasthenia gravis	2 (1)
							Encephalopathy – unspecified	6 (3)
							Other	16 (8)
	Total	122 (100 %)		65 (100 %)				204 (100 %)

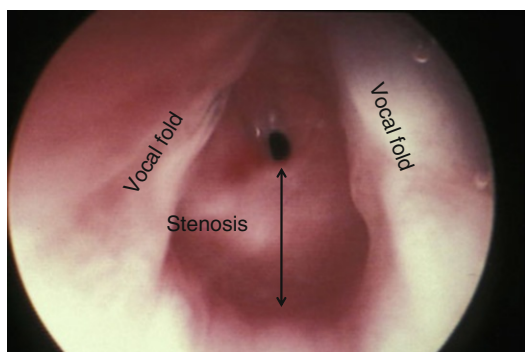


Fig. 56.4 Endoscopic view of subglottic stenosis, with severe narrowing of the airway below (distal to) the level of the vocal folds. This child has a tracheotomy in place below the stenosis

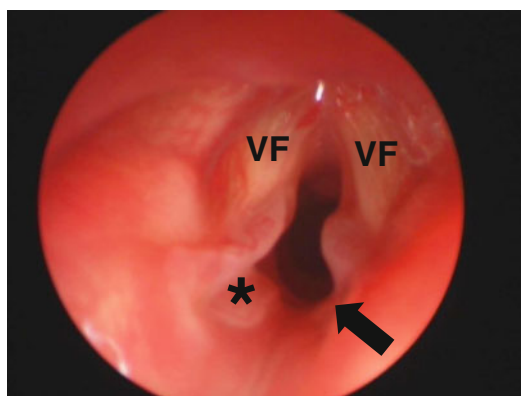


Fig. 56.5 Endoscopic view of acute laryngeal trauma in a 2-month-old ex-premature gestation infant. Note edema and erythema of vocal folds (VF), granulation tissue at the left posterolateral glottis (*), and erosive lesion at the right posterolateral aspect of the glottis (arrow)

56.3 Clinical Practice and Experience

In adults, early tracheotomy is variously defined as a tracheotomy within 2–10 days of intubation in selected patients, generally when prolonged intubation is anticipated (McWhorter 2003). Defining the duration of “prolonged intubation” in infants is difficult as some infants tolerate intubation for weeks to months without adverse laryngeal effects (McWhorter 2003), but extended periods of intubation do interfere with normal development and can contribute to laryngotracheal damage. National surveys reveal that elective tracheostomy is rarely performed among children requiring mechanical ventilation in Canada. However, >50 % of these critical care physicians believe tracheostomy is underutilized (Principi et al. 2008). Interim endoscopic evaluations, and possibly optical coherence tomography in the future, may help distinguish patients with findings suggestive of reversible edema versus findings suggestive of significant, irreversible subglottic damage (Ridgway et al. 2008) (Fig. 56.5).

Studies in adults demonstrate that tracheotomies are more comfortable than prolonged intubation. In a study of adult intensive care unit patients expected to require mechanical ventilation for more than 7 days, Blot et al. surveyed surviving and conscious patients; all 45 respondents who had undergone both trans-laryngeal intubation

and early or late tracheotomy considered that the tracheotomy was the most comfortable technique (Blot et al. 2008). Nieszkowska et al. used indirect measurements of comfort and found that after tracheotomy, adult mechanically ventilated intensive care unit patients required less intravenous sedative administration and spent less time heavily sedated (Nieszkowska et al. 2005). Although it is likely that a tracheotomy is also more comfortable than endotracheal intubation for children, we were unable to identify similar studies evaluating children (Principi et al. 2008).

Compared with endotracheal intubation, tracheotomies provide a variety of developmental and social advantages. Early mobilization for acute lung injury and prevention of neuromuscular wasting are an evolving consideration (Schweickert et al. 2009). Even if they continue to require ventilator support, children with tracheotomies can participate in a variety of activities not possible during intubation, such as physical, swallowing, speech, and other therapies. They have greater freedom of movement, and can be held by family or healthcare providers to facilitate bonding and soothing, without concern for unintentional extubation. Finally, having a tracheotomy allows a greater variety of placement options for individual children, including the potential to receive care in their own homes or in a rehabilitation or chronic care facility, as

Table 56.2 Potential complications directly or indirectly related to tracheotomy in children Mahadevan et al. (2007); Davis (2006); Deutsch (1998); Carr et al. (2001)

Intraoperative risks	Early postoperative risks	Long-term risks
Lack of airway control	Unintended decannulation, inability to recannulate because stoma tract is immature	Unintended decannulation, inability to recannulate
Inability to ventilate		Suprastomal collapse; tracheomalacia
Pneumothorax		Stomal granulomata
Esophageal injury		Tracheocutaneous fistula persisting after decannulation
	Lower respiratory tract infections, aspiration pneumonia	
	Ventilatory failure caused by air leak around the tube	
	Tracheitis	
	Stomal cellulitis, bleeding, breakdown	
	Neck skin erosion	
	Subglottic stenosis	
Tube occlusion		
Hemorrhage		
Creation of false passage		
Disconnection or other problems with tracheotomy tubing and ventilator		
Interstitial air (emphysema, pneumomediastinum, pneumothorax)		
Respiratory arrest, cardiac arrest, death		

few of these options are available to children who are intubated.

In children, the tracheotomy procedure is most frequently performed in an operating room, with the patient intubated and receiving general anesthesia. Uncommon exceptions to this include some children with acute laryngeal trauma, and percutaneous tracheotomy has also been reported (Principi et al. 2008). Risks of undergoing tracheotomy can be considered as those occurring during the surgical procedure and those occurring in the postoperative period and long-term risks. Risks directly or indirectly related to the tracheotomy are listed in Table 56.2. Tracheotomy tube occlusion is a common problem, occurring at a rate of up to 72 % of premature and newborn children with tracheotomies and, less frequently, at a rate of up to 14 %, in children 1 year and older (Davis 2006). The higher rate in younger children is likely related to the narrow inner radius of small tracheotomy tubes and the common condition of bronchopulmonary dysplasia, with concomitant viscous bronchial secretions, in premature infants (Davis 2006).

In Davis' review, the overall risk of mortality in children with a tracheotomy was 18 %, usually from unrelated causes (Davis 2006). Mahadevan notes 2 deaths from tracheotomy-related complications in their series of 122 pediatric tracheotomies performed over 17 years: 1 from early acute respiratory arrest and 1 from accidental decannulation

in the community (Mahadevan et al. 2007). Carron reported 6 deaths, with a mortality of 3.6 %; 4 of these deaths were related to plugging of the tracheotomy tube with resultant respiratory arrests occurring between 0.3 and 30.8 months after surgery (Carron et al. 2000).

56.3.1 Tracheotomy Tube Changes

The first tracheotomy tube change should be performed by the surgeon, to confirm that the stoma is sufficiently healed. This can be done as early as 3 days postoperatively (Deutsch 1998) but is commonly done 5–7 days after surgery; timing is at the discretion of the surgeon. “Stay sutures” are often placed in the anterior tracheal wall at the time of surgery, on the left and the right sides of the incision into the tracheal cartilages, and are then taped to the skin surface, on the left and right sides of the chest, respectively. In the event of the early need for recannulation, before the stoma is healed or mature, gently pulling these sutures anteriorly and laterally (e.g., away from the stoma, in their respective directions) helps to lift the trachea closer to the surface of the neck and simultaneously open the incision to facilitate recannulation. If stay sutures were placed, they are generally removed after the first successful tube change. Once the stoma is considered stable, tracheotomy tube changes can

be delegated to appropriately trained providers, including family members as well as professional healthcare personnel.

Preparation is an important aspect of replacing the tracheotomy tube, whether circumstances are elective or emergent, and includes access to an assistant, appropriate monitoring, gathering the appropriate equipment and supplies, optimiz-

ing the child's position, and, as appropriate, pre-oxygenating the child and deflating the cuff of the tracheostomy tube. Although supplies should be sterile or sterilized before use, they can generally be handled in a clean manner. Resources to implement a backup plan should be immediately available, particularly for new tracheotomies or patients with challenging anatomy. See Fig. 56.6

Removing a tracheotomy tube

Gather the appropriate equipment and supplies, as well as another person to assist

- Tracheotomy tube, with obturator
- Tracheotomy tube one size smaller, with obturator
- Suction catheter
- Scissors
- Neck roll
- Lubricant
- Trach ties
- Supplemental oxygen (depending on the child's needs)

Wash your hands and wear gloves; handle supplies and equipment in a clean manner

Prepare the replacement tracheotomy

- Insert the obturator
- Lubricate the tip of the tracheotomy tube
- If a cuff is present, make sure it is deflated and smooth
- Put the replacement tracheotomy tube and the spare tube in an accessible location
- Stand at the side of the patient's neck and

Mentally rehearse both removing and replacing the tracheotomy

Position the patient, including placing a shoulder roll to extend his or her neck

Have an assistant provide adequate restraint if the child is unable to cooperate

Suction the existing tracheotomy and optimize oxygenation if needed

Deflate the tracheotomy cuff (if present)

Release the trach ties but hold the flanges against the patient's neck to control the tracheotomy tube

Consider that the cuff may have bulk that must fit through the stoma

Anticipate a curved motion of your hand

Gently remove the tracheotomy tube, following and remembering the curve created by the shape of the tube and its pathway. Feel this curve as you remove the trach; make a mental memory of the motion

Reinserting a tracheotomy tube

Remember the curved motion of the tube removal, and anticipate that curve in reverse

Follow the curve as you replace the tracheotomy tube

Stabilize the tube by holding the flanges

Immediately remove the obturator

Confirm appropriate placement by checking for

- Air flow
- Appropriate breath sounds
- The child's comfort
- The presence of end – tidal CO₂ (this may not be available in all settings)

Secure the tracheotomy tube around the child's neck

It should be snug but not tight; check both the left and the right side of the neck

Fig. 56.6 These are the basic steps involved in removing and replacing a tracheotomy tube

for a description of a typical tracheotomy tube change. Practicing so that the steps are fluid is important.

There are several tactics that may be useful if a tracheotomy tube change becomes difficult or is anticipated to be difficult. Make sure that the patient is optimally positioned and controlled, including neck extension, and that the obturator is in place in the tracheotomy tube which is to be inserted. If attempts to replace the child's normal tracheotomy tube are unsuccessful, especially if there is bleeding or edema, it may be feasible to insert a smaller tracheotomy tube. Another option is to use a Seldinger technique, in which a tracheotomy tube without an obturator is threaded over a suction catheter; the catheter is used to find and secure the pathway through the stoma into the trachea, and then the tracheotomy tube is advanced into the trachea over the suction catheter. Simultaneous provision of oxygen flow can be helpful to prevent desaturation, and confirmation with end-tidal CO₂, when available, is helpful.

Simulation can be used to teach some tracheotomy-related surgical skills, as well as for teaching parents how to identify and manage problems related to the tracheotomy. Physical models using drilled "holes" which travel in a straight (rather than curved) trajectory in the neck of the model lack the appropriate anatomic feel of the naturally downward curve of the tract between the stoma and the trachea.

56.4 Specific Considerations When Ventilating a Patient with a Tracheostomy

Principles of mechanical ventilation for the infant or child with a tracheostomy are identical to the approach for the same child with an endotracheal tube. As with endotracheal tubes, appropriately securing the tube and ensuring tube patency remain important. Additional considerations unique to tracheostomy care include decisions about tracheostomy tube size and whether a cuff is indicated.

56.4.1 Make Sure the Size of Tracheostomy Tube Is Optimized

Most chronically mechanically ventilated children use the smallest tube practical, to allow for vocalization around the tube while the child is "healthy." It is often necessary to "upsized" the tracheostomy tube by 0.5 to 1 mm if there is a large air leak, frequent plugging of the tube, or high inspiratory or expiratory resistance of the large airways.

56.4.2 If There Is a Cuff, Make Sure It Is Not Under- or Overinflated

Overinflation of the cuff can cause the cuff to herniate around the tip of the cuff and occlude the airway. Overinflation of the cuff can also exert transmural pressure that can impede local tracheal mucosal blood flow and predispose to ischemia, scarring, and subglottic stenosis. For this reason, tracheal cuff pressures should be monitored periodically and inflated to allow a leak at a pressure that is not excessive, usually less than 25 cm H₂O pressure (Newth et al. 2004; Khine et al. 1997; Deakers et al. 1994; Mossad and Youssef 2009; Mhanna et al. 2002; Weiss et al. 2009; Browning and Graves 1983; Dorsey et al. 2010).

56.4.2.1 Arguments Against Inflated Cuffed Tracheostomy Tubes

1. Use of a cuffed tube may require selection of a smaller tube for age (0.5 mm), which increases the airway resistance and potentially increases the effort required during spontaneous breathing and the risk for tube plugging/occlusion.
2. Requires close monitoring to limit excessive tracheal wall pressure, which could injure the mucosa and risk for tracheal stenosis.
3. Inhalation anesthetics (e.g., nitrous oxide) may increase volume and pressure in cuff over time.

4. As the stoma will eventually shrink to the size of the tracheostomy tube shaft, a cuff may add to the width of the tube and can cause trauma to the stoma during tracheostomy tube changes. This problem is minimized in modern tubes which have slim cuff profiles when the cuff is deflated.

56.4.2.2 Arguments for Inflated Cuffed Tracheal Tubes

1. Occlusion of air leak may improve ability to achieve lung expansion, square wave flow delivery, peak inspiratory pressure, or PEEP, when there is poor lung compliance.
2. Monitoring of lung function, tidal volumes, metabolism, and exhaled CO₂ and medical gases (e.g., NO, isoflurane) is more reliable.
3. Minimizes contamination of the environment with anesthetic gases (e.g., isoflurane).
4. Modern tracheotomy cuffs have low pressure when properly inflated.
5. Use of less fresh gas flow is potentially cost saving.

Several sentinel studies using modern low-pressure, high-volume cuffs have supported the use of cuffed endotracheal tubes during invasive mechanical ventilation (Newth et al. 2004; Khine et al. 1997; Deakers et al. 1994). Pediatric case series, small case-control studies, and observational cohort studies (Newth et al. 2004; Deakers et al. 1994; Mossad and Youssef 2009; Mhanna et al. 2002) suggest that cuffed tracheal tubes can be used without increasing the risks for developing subglottic stenosis in patients having surgery for congenital heart surgery or other selected conditions (Weiss et al. 2009; Dorsey et al. 2010); and a small case-controlled study (Browning and Graves 1983) showed that cuffed tracheal tubes decreased the incidence of aspiration in the pediatric ICU.

56.4.3 Make Sure the Tracheal Tube Is Patent and Not Obstructed

Evaluate and monitor the patency of the tracheostomy tube using clinical signs (e.g., chest

wall movement, breath sounds, and humidity in the tube) and quantitative exhaled CO₂ (e.g., capnography). Pass an appropriately sized suction catheter to just past the distal tip of the tracheostomy tube. If there is any doubt about patency or partial occlusion or coating, **CHANGE THE TRACHEOSTOMY TUBE** to a new tube. Obstruction is the most common cause of decompensation. If the tube is patent and has been changed, and the obstruction seems to be positional or intermittent, consider that a tracheal shelf or redundant tracheal tissue may obstruct the tube as it abuts the wall of the trachea. In these circumstances, a slightly longer tracheal tube which passes beyond the area of occlusion is sometimes helpful. Safe insertion of the tube beyond the area of narrowing is easiest when guided by fiber-optic tracheoscopy or bronchoscopy. If you have difficulty finding an appropriately sized or length tracheostomy tube, consider temporarily replacing the tracheostomy tube with standard cuffed endotracheal tube inserted through the stoma site.

56.4.4 Make Sure the Tracheostomy Tube Is Appropriately Secured

Make sure that the tracheostomy tube ties around the neck are secure and snug, but not so tight as to occlude the jugular venous drainage or cause superior vena cava syndrome. Tracheotomy ties which incorporate elastic and “hook and loop” fasteners (e.g., Velcro™) often work well. In some patients, a second set of ties, extending under the axillae and across the back, will stabilize the tracheotomy; these ties do not have to be as tight as the neckties.

Make sure the connections to the mechanical ventilator are secure, and insert extension tubing (short) if the connection is pulling on the stoma site. If the exhaled CO₂ is very high or ventilation is extremely compromised, double-check that too much extension tubing has not been inserted between the tracheostomy and the ventilator.

If unusual movement or positioning is required (e.g., internal jugular vein vascular catheterization, prone positioning, ECMO cannulation), consider suturing the tracheostomy tube in place, but make sure to have scissors or scalpel close by, in case urgent replacement of the tube is required.

Essentials to Remember

The management of pediatric and neonatal mechanical ventilation is generally the same for patients with tracheostomy tubes as it is for standard endotracheal tubes:

- Ensure that the tube is of the optimal size.
- Check and adjust the cuff inflation.
- Check the patency of the tube and the airway clinically, and document exhaled CO₂.
- Make sure the connections to the tube are secure.
- Do not hesitate to exchange the tube.
- Always be prepared with suction, sedation, monitoring, positioning, and a spare tracheostomy tube of the same and smaller diameter.

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Part XXII

Weaning from Mechanical Ventilator Support

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Educational Goals

- Understand the goals for weaning from mechanical ventilation.
- Identify the predictors used to assess weaning readiness.
- Understand the methods of weaning from mechanical ventilation.
- Identify the indices used to predict extubation readiness and their limitations.
- Identify the key elements of extubation success.

Studies in developed countries have shown that between 23 and 40 % of children in the pediatric intensive care unit (PICU) receive mechanical ventilator support during their PICU stay (Dahlem et al. 2003; Watson et al. 2002; Angus et al. 2001; Census 2002; Farias et al. 2006; Khemani et al. 2007; Curley et al. 2005). The weaning phase of

mechanical ventilator support has been defined as the “transition from ventilatory support to complete spontaneous breathing while maintaining effective gas exchange” (Newth et al. 2009). Extubation is the physical removal of the endotracheal tube and is the endpoint of the weaning phase. On average, the weaning phase accounts for approximately 40 % of the total duration of mechanical ventilation in children (Newth et al. 2009; MacIntyre 2001).

The goal for weaning from mechanical ventilation is to liberate the child from the ventilator as soon as he/she is able to sustain independent breathing. This is to minimize the many risks associated with mechanical ventilation, including ventilator-associated lung injury, ventilator-associated pneumonia (VAP), and upper airway injury to the trachea and vocal cord area (Rivera and Tibballs 1992; Jorgenson et al. 2007). Unfortunately, there are no completely accurate and reliable indicators of a patient’s ability to be successfully extubated (Watson et al. 2002). Premature extubation is also associated with increased morbidity such as aspiration, complications of reintubation, and higher rates of VAP (Jorgenson et al. 2007). Identifying a patient’s readiness to wean and extubate can significantly reduce the overall duration of mechanical ventilation (MacIntyre 2001). In this chapter, we will review what is known about effective methods of weaning children in the PICU from mechanical ventilator support and indicators to assess readiness for extubation.

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57.1 Identifying Weaning Readiness and Need for Weaning

In 2001, a task force of clinicians from the American College of Chest Physicians, the American Association for Respiratory Care, and the American College of Critical Care Medicine reviewed the existing evidence and published guidelines for weaning and discontinuation of ventilatory support for mechanically ventilated adults (MacIntyre 2001). The guidelines recommended that the practitioner first reverse all possible causes contributing to ventilator dependence including (a) neurologic and neuromuscular conditions contributing to weakness such as oversedation and critical illness neuropathy and myopathy, (b) cardiac issues that interfere with pulmonary function including poor cardiac function with inability to sustain the workload of independent breathing and cardiogenic pulmonary edema, (c) poor nutritional status with insufficient caloric intake to sustain the extra workload, and (d) fluid overload. Once these causes are reversed to the extent possible, the patient must show proof of adequate oxygenation and hemodynamic stability. Finally, the patient must be capable of spontaneous breathing with sufficient muscle strength and optimal neurologic alertness. Although no evidence-based or consensus guidelines exist for weaning and discontinuing mechanical ventilator support in children, the above criteria for initiation of weaning appear reasonable across all ages.

Historically, it was thought that because many patients become weak while on extended mechanical ventilator support, in part due to muscle atrophy, gradual weaning was necessary to optimize retraining and rehabilitation of the respiratory muscles. Since the 1990's, multiple clinical studies have shown that patients may not require a gradual wean from ventilatory support and are ready to extubate as soon as they pass a "test" for extubation readiness. The patients would undergo the testing as soon as they met the criteria for initiating weaning as listed above,

were spontaneously breathing over the set ventilator rate, could maintain adequate oxygenation on a reasonable amount of delivered FiO_2 (40–60 %, depending on the study), and had acceptable hemodynamics, usually no longer requiring vasopressor support.

In adults, a spontaneous breathing trial (SBT) has been used in multiple mechanical ventilator weaning studies (MacIntyre 2001; Randolph et al. 2002; Esteban et al. 1995, 1997, 1999; Brochard et al. 1994; Farias et al. 2002, 2001; Chavez et al. 2006; Thiagarajan et al. 1999; Leclerc et al. 2002; Carlucci et al. 2009; Jounieaux et al. 1994). Adults who tolerate SBTs for 30–120 min more often than not will be extubated successfully, with success defined as not requiring reinstitution of mechanical ventilator support for 24 or 48 h, depending on the study (MacIntyre 2001). The criteria to tolerate an SBT are usually multiple and include physiologic parameters to define adequate gas exchange, respiratory pattern, hemodynamic stability, and signs or symptoms of distress. For oxygenation, most SBT trials use an amount of FiO_2 that could easily be delivered by a mask once the patient is extubated (40–50 %) and require pulse oximetry saturations to be maintained at ≥ 93 % or ≥ 95 %. Indicators of the ability to sustain adequate ventilation include the ability to maintain tidal volumes ≥ 5 ml/kg ideal body weight on minimal to no support, a $\text{PaCO}_2 \leq 50$ mmHg or ≤ 10 mmHg increase from the level prior to the SBT, arterial pH ≤ 7.30 , and respiratory rate in the acceptable range for age. Other indicators include normal systolic blood pressure for age without the use of vasopressors, stable mental status with sufficient alertness to maintain the airway, tolerable levels of discomfort, and no diaphoreses, severe agitation, or other signs of extreme stress. If the patient fails an SBT, ventilation is continued and the SBT is repeated in 24 h as long as the patient maintains criteria for weaning. The SBT could be repeated sooner if reversible causes of failure, such as oversedation, have been corrected. Studies using 30 min SBTs had similar outcomes to those using 120 min SBTs (Esteban et al. 1999). In adults, the test can be performed with the patients on a T-piece, continuous positive airway pressure

(CPAP), or a low level of pressure support such as 4–5 cm H₂O (MacIntyre 2001).

Based upon the literature in adult patients, investigators from the Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network developed and tested an “extubation readiness test” or ERT in children (Randolph et al. 2002). Of the 313 children tested for extubation readiness, 41.8 % passed the ERT prior to starting a weaning mode, and of these, 74 % were successfully extubated (Randolph et al. 2002). In a large RCT by Farias et al. (2002), 77 % of children tested with a spontaneous breathing trial passed on the first attempt and were extubated without weaning. As seen in adults, pediatric patients can be extubated without weaning.

57.2 Methods of Weaning

There are many methods used to wean children from mechanical ventilatory support. There are no studies showing that one mode of weaning children from mechanical ventilatory support is superior. Pressure support ventilation is commonly used as a weaning mode and allows the patient to initiate and terminate the breath in synchrony with the ventilator (Randolph et al. 2002). The pressure support level is gradually decreased, and extubation readiness is tested from a “low” level of support. Volume-assured pressure support and volume support are forms of pressure support that guarantee a set volume of support per assisted breath. The pressure to maintain a given breath is decreased automatically over time as the respiratory mechanics improve, and theoretically, weaning in this mode is semiautomated. Another mode commonly used in weaning children from mechanical ventilation is synchronized intermittent mandatory ventilation or SIMV. In this mode, the set SIMV rate is slowly decreased with the patient breathing spontaneously in between the SIMV breaths. Spontaneous breaths may or may not be supported with pressure support.

Another method of weaning from mechanical ventilation is to alternate periods of ventilatory support with graded periods of spontaneous

breathing, called “sprinting.” This method is most often used in patients who have acute or chronic lung disease with a tracheostomy in place. Many of these patients are weak, and theoretically, the muscle fibers are retrained by intermittent and increasingly prolonged periods of high workload interspersed with rest. Adult patients failing multiple weaning attempts were found to have a reduced maximum transdiaphragmatic pressure compared to those able to successfully wean from mechanical ventilation whereas those able to successfully wean following a rehabilitation period had improved transdiaphragmatic pressures and load/capacity ratio (Carlucci et al. 2009). There is conflicting evidence whether retraining the diaphragmatic musculature decreases the duration of mechanical ventilation. Small studies have shown improved weaning duration with inspiratory muscle training in adults (Martin et al. 2002).

Randolph and colleagues in the PALISI Network randomized 182 children who had initially failed an ERT to a pressure support protocol (shown in Table 57.1), a volume support protocol or to “standard care” where weaning was directed by their clinical team (Randolph et al. 2002). The pressure support and volume support protocols required daily ERTs in patients until the ERT was passed. Most of the children in the study had respiratory failure from acute respiratory infections. In the standard care arm, clinicians used a mix of SIMV, SIMV/pressure support, and pressure support alone. No differences in duration of mechanical ventilation were found between the three arms of the trial. Of note, the median duration of weaning was ≤ 2 days in all three arms of the trial. It is possible that the method of weaning children from mechanical ventilator support may be more important in those children who have a more prolonged duration of weaning and have muscle weakness. In adults, weaning protocols have been shown to improve the duration of mechanical ventilation. In a Cochrane Review comparing protocolized to non-protocolized weaning from mechanical ventilation, protocolized weaning reduced the duration of mechanical ventilation by 25 % and the duration of weaning by 78 % (Blackwood et al. 2010).

Table 57.1 Pressure support weaning protocol and extubation readiness test used in a prior randomized controlled trial comparing three methods of weaning children from mechanical ventilator support (Randolph et al. 2002)

PRESSURE SUPPORT WEANING PROTOCOL	
<i>Physician to review in entirety in conjunction with a Respiratory Therapist</i>	
☐ Patient is on a ventilator that delivers pressure support ☐ Physician to review pain and sedation orders with RN ☐ PEEP $\leq$ 7 cm H ₂ O and FiO ₂ $\leq$ 60% ☐ Check inspiratory rise time and flow sensitivity (adjust if necessary)	
INITIATE PRESSURE SUPPORT	PATIENT'S IDEAL BODY WEIGHT: _____ KG
PS min by ETT size: 3.0 to 3.5 ETT = 12 cm H ₂ O; 4.0 to 4.5 = 10; 5.0 to 5.5 = 8; $\geq$ 6.0 = 6 cm H ₂ O	
ETT size = _____	PS min = _____ cm H ₂ O
1. Change to PS mode on PS min + 2 cm H ₂ O 2. Adjust PS to achieve exhaled VT of 5-7 ml/kg (_____ to _____ ml) and hold for 4 hours.	
ADJUST FIO₂ AND PEEP	
Maintain SpO₂ $\geq$ 95%	
- If SpO₂ $\geq$ 95% on FiO₂ $\leq$ 0.60, decrease PEEP by 1 cm H₂O Q4 hours (PEEP $\geq$ 8 cm H₂O for > 4 hrs = weaning cessation, see back of page) - Once PEEP is $\leq$ 5 cm H₂O, then wean FiO₂ to $\leq$ 50%	
<i>If SpO₂ < 95%, then return to previous setting, notify MD, and hold PEEP wean for 4 hrs.</i>	
PRESSURE SUPPORT ADJUSTMENT	
Goal is to wean to PSmin keeping exhaled VT between 5 to 7 ml/kg	
- If exhaled VT $\geq$ 7 ml/kg (_____ ml) at any time OR VT $\geq$ 5 ml/kg (_____ ml) for $\geq$ 4 hours then wean PS by 2 cm H₂O and reassess in 30 minutes. Evaluate Q4 hrs. - See EXTUBATION READINESS. When PSmin (_____) is reached, see Extubation at bottom of page. - If exhaled VT are consistently < 5 ml/kg (_____ ml) then increase PS in 2 cm H₂O increments to achieve tidal volumes of $\geq$ 5 ml/kg AND do not wean PS for at least 4 hours. <i>Spontaneous RR goal: age > 5 years (10 to 35 bpm); age 2-5 years (15 to 40 bpm); age 6 months to 2 years (15 to 45 bpm); age < 6 months (20 to 55 bpm)</i> - RR is > RR goal? → YES: (a.) Could be from anxiety alone. Evaluate sedation/analgesia. (b.) If anxiety appears to be from excessive work of breathing, increase PS 2 cm H₂O until RR is in range. - RR is < RR goal? → YES: If oversedated, decrease sedation/analgesia.	
EXTUBATION READINESS	
☐ PS $\leq$ 16 cm H ₂ O and SpO ₂ $\geq$ 95% on PEEP $\leq$ 5 cm H ₂ O and FiO ₂ $\leq$ 0.50 for a minimum of 4 hours If the above criteria are met, once every 24 hours with Physician approval you may perform an Extubation Test by placing patient on PS min (_____) and monitoring exhaled tidal volumes.	
If exhaled tidal volume is consistently < 5 ml/kg (_____ ml) AND/OR SpO ₂ < 95 % on PEEP $\leq$ 5 and FiO ₂ $\leq$ 0.50 AT ANY TIME , then return to previous PS setting, hold for 4 hours then decrease stepwise to PSmin as specified in PRESSURE SUPPORT ADJUSTMENT above.	
Extubation	
Once patient is on PSmin and for $\geq$ 2 hours (1.) Exhaled tidal volumes are $\geq$ 5ml/kg AND (2.) SpO ₂ $\geq$ 95% on PEEP $\leq$ 5 and FiO ₂ $\leq$ 0.50, then proceed to Extubation	

Cumulative fluid balance and sedation have both been implicated in prolonged duration of mechanical ventilation. Positive fluid balance is associated with increased duration of

mechanical ventilation in adults and children (Weidemann et al. 2006, Valentine et al. 2012). In a large multicentered RCT, a conservative fluid management strategy significantly reduced the

duration of mechanical ventilation in subjects with ARDS ($p < 0.001$) (Weidemann et al. 2006) when compared to a liberal fluid management strategy. This effect has been seen in multiple studies, indicating that careful attention must be paid to fluid balance in injured lungs to decrease the length of mechanical ventilation (Weidemann et al. 2006; Flori et al. 2011; Willson et al. 2013). Sedation has also been implicated in increased duration of mechanical ventilation in children (Randolph et al. 2002). Sedation protocols aimed to standardize sedation practice reduce the duration of mechanical ventilation, with absolute reductions in the duration of mechanical ventilation ranging from 10 to 70 % depending on the study and may decrease the duration of weaning as well (Jackson et al. 2010).

57.3 Assessing Patients' Readiness to Extubate

As described previously, there are three methods of spontaneous breathing trials, T-piece trials, CPAP trials, and minimal PS trials (MacIntyre 2001). In the T-piece trial, the patient is removed from the ventilator, and humidified oxygen is provided through the T-piece. The flow should provide constant mist during both inspiration and expiration to match the patient's minute ventilation. The minimal pressure support technique provides a minimal amount of pressure support estimated to overcome the resistance to breathing through an artificial airway and adjusted higher for smaller diameter endotracheal tubes. In CPAP trials, the patient is placed on a CPAP level of 4–5 cm H₂O. During all of these SBTs, indicators of oxygenation, ventilation, work of breathing, and patient distress are monitored.

Adult studies have demonstrated success using the spontaneous breathing trial and, more importantly, have shown that many patients are ready to be extubated without the need to wean. In a large RCT by Esteban et al. (1995), 76 % of patients evaluated for weaning readiness were extubated without weaning. In patients that failed an initial extubation evaluation, weaning

methods were compared using daily T-piece trials, multiple SBTs, PSV, and intermittent ventilation. Patients were extubated successfully three times faster with a spontaneous breathing trial compared to intermittent ventilation and two times faster compared to pressure support ventilation (Esteban et al. 1997). Brouchard et al. (1994) compared weaning modalities using a T-piece, PSV, and SIMV. More patients were successfully weaned with PSV compared to SIMV. There was no difference in the rates of reintubation using PS compared to T-piece; however, more patients tolerated the PS trial and were extubated than the T-piece trial.

The ERT used by the PALISI Network in children consisted of first testing oxygenation and then, if oxygenation could be sustained on extubatable settings (FiO₂ 0.5, PEEP 5 cm H₂O), testing ventilatory support needs. The FiO₂ was dropped to 0.5 and the PEEP to 5 cm H₂O. If the patient was previously at these settings and maintaining peripheral oxygen saturations (SpO₂) ≥ 95 % on pulse oximetry, the settings were left unchanged. Patients unable to maintain an SpO₂ of ≥ 95 % failed the test. Those who maintained an SpO₂ of ≥ 95 % were placed on minimal PSV. Minimal pressure support was adjusted for the ETT size because of increasing resistance with lower ETT size (pressure support of 10 cm H₂O for an ETT size 3.0–3.5, 8 cm H₂O for an ETT size 4.0–4.5, and 6 cm H₂O for an ETT size ≥ 5.0). Exhaled tidal volumes were measured at the ETT with neonatal, pediatric, or adult sensors. Patients were monitored during the test for 2 h. Patients were classified as failing the test if at any time in the 2-h period their SpO₂ was less than 95 %, their exhaled tidal volume was less than 5 ml/kg ideal body weight, or their respiratory rate was outside of the acceptable range for their age (20–60/min for age ≤ 6 months, 15–45/min for 6 months–2 years, 10–35/min for age 2–5 years). As soon as any criteria for failure were met, the patient was removed from the test, placed back on previous ventilator settings, and randomized to PSV, VSV, or no protocol.

There are other studies of SBTs in children. In a large RCT by Farias et al. (2002), 77 % of children tested with a spontaneous breathing trial

passed on the first attempt and were extubated without weaning. Like adults, the data supports that many pediatric patients are extubated successfully without weaning. In patients that failed an SBT, Farias et al. (2001) compared weaning modalities using pressure support of 10 cm H₂O to T-piece alone. There were no differences in 48 h extubation failure rates between the two groups. Respiratory rate, tidal volume, RSBI, and maximal negative inspiratory pressure (PI_{max}) were all poor predictors of extubation outcome. Chavez et al. (2006) evaluated the use of a 15 min SBT trial to test for extubation readiness. The SBT consisted of delivery of a continuous flow of oxygen sufficient to deliver a CPAP of 5 cm H₂O. Patients were tested when they were deemed ready to be extubated, rather than ready to be weaned. Ninety-one percent of patients passed the initial trial and were extubated; 7.8 % failed extubation. These studies indicate that the majority of children are ready to be extubated without the need to wean.

57.4 Predictive Indices of Extubation Success

The 2001 task force identified eight specific predictors of extubation used in the literature, with varying predictive abilities, as shown in Table 57.2 (MacIntyre 2001). These indices were minute ventilation (V_E) 10–15 l/min, negative inspiratory force (NIF) 20–30, maximal inspira-

tory mouth pressures (PI_{max}) –15 to –30, airway occlusion pressure (P₀₁)/PI_{max} (0.30), CROP score (dynamic compliance × maximal negative inspiratory pressure × (PaO₂/PAO₂)/respiratory rate), respiratory rate (RR) 30–38 breaths per minute (bpm), tidal volume (VT) 325–408, and rapid shallow breathing index or respiratory rate/VT ratio 60–105. Of these variables, RSBI <100 breaths/min/l, the CROP index, RR >38 bpm, tidal volume standardized to body weight, and NIF 20–25 H₂O had the greatest predictive potential. The CROP index, RR, RSBI, and VT are indices that have been used in children (Newth et al. 2009).

In pooled adult studies, a RSBI <100 or 105 breaths/min/l had a sensitivity of 65–96 % and a specificity of 0–73 % to predict successful extubation. Respiratory rate (RR) <38 bpm had a sensitivity of 88 % and a specificity of 47 %. When both were pooled together, a RR >38 bpm and an RSBI <100 reduces the probability of successful extubation. Given the high sensitivity but low specificity, the RSBI and RR indices may help screen those ready for extubation (Newth et al. 2009; MacIntyre 2001). Thiagarajan et al. (1999) evaluated potential predictors of extubation readiness in children. A RR ≤45 bpm, spontaneous tidal volume ≥5.5 ml/kg, RSBI ≤8 breaths/min/ml/kg body weight, and the CROP index ≥0.15 ml/kg body weight/breaths/min were good predictors of successful extubation. Leclerc et al. (2002) found the CROP index and the RSBI to have sensitivities of 97 and 94 %, respectively,

Table 57.2 Indices used to predict extubation success following a spontaneous breathing trial in adults (MacIntyre 2001)

Indices	Definition	Range in adults
V _E	Minute ventilation	10–15 l/min
NIF	Negative inspiratory force	–20 to –30 cm H ₂ O
PI _{max}	Maximal inspiratory pressure	–15 to 30 cm H ₂ O
P ₀₁ /PI _{max}	Mouth occlusion pressure 0.1 s after the onset of respiratory effort	0.30
CROP index	Dynamic compliance × maximal negative inspiratory pressure × (PaO ₂ /PAO ₂)/respiratory rate	13
VT	Tidal volume	325–408
RSBI or f/VT	Rapid shallow breathing index or ratio of respiratory rate/tidal volume	60–105
RR	Respiratory rate	30–38 bpm

with a specificity of 0 % in both. The area under the ROC curve was 0.8, suggesting that neither was a good predictor of extubation success. Manczur et al. (2000) found tidal volume and minute volume to be the best predictive indicator of extubation success, with low tidal volumes and minute volumes being the most predictive of extubation failure. In adults, poor cough strength and magnitude of endotracheal secretions has also been used (Khamiees et al. 2001). Cough strength was measured subjectively and objectively by measuring a patient's ability to propel secretions onto a card placed 1–2 cm away from the endotracheal tube. Cough strength predicted extubation failure with a RR of 31.9 % (95 % CI 4.5–225 %). Despite the many indices used to predict extubation success, in multiple studies, none used individually have been shown to be superior to clinical judgment.

57.5 Extubation Failure

In a multicenter prospective study evaluating intubation and extubation practices of children receiving mechanical ventilation for over 48 h, 6.2 % of subjects were reintubated in 24 h. The mean duration of mechanical ventilation was 4.8 days [3–7 days] (Kurachek et al. 2003). In those that failed extubation, patients age <24 months with chronic respiratory disorder, chronic neurologic condition, or a genetic syndrome were at higher risk. Patients failing extubation had higher mortality rates and longer PICU lengths of stay. Other studies in children report extubation failure rates of 4 % (Baisch et al. 2005). Younger children are at highest risk of extubation failure. Children who fail extubation have longer hospital stays but no difference in mortality (Baisch et al. 2005).

Upper airway obstruction accounts for the largest category (37 %) of failed extubations. In a prospective, blinded, cohort study, Wratney et al. (2008) evaluated the airway leak test to predict upper airway obstruction and extubation failure in critically ill infants. The leak test assesses air flow around the endotracheal tube and helps to provide information on potential soft tissue

edema in the airway. Pressure is applied between 20 and 25 cm H₂O while listening for airflow or “air leak” around the endotracheal tube. A leak is determined absent if there is no airflow at a pressure of 30 cm or less. In this cohort, an air leak was absent in 47 % of patients. Of those without a leak, 82 % were extubated successfully suggesting that the air leak test is a poor indicator of extubation failure (Wratney et al. 2008).

Identifying a patient's readiness for weaning and extubation is crucial in reducing the risk of mechanical ventilation. A spontaneous breathing trial should be initiated in patients as soon the patient is ready to be weaned. Many patients can be successfully extubated without weaning. Predicting those who will be successfully extubated following a successful spontaneous breathing trial is difficult. There is no one test to reliably predict successful extubation in all patients. Of those patients that require weaning from mechanical ventilation, no one method of weaning is superior; however, utilizing a weaning protocol may help to reduce overall weaning duration. Protocols and tests for extubation readiness can help guide the clinician in judging a patient's potential success for extubation. Future studies are needed to develop and test indicators of weaning and extubation readiness in children.

Essentials to Remember

- The goal for weaning from mechanical ventilation is to liberate the child from the ventilator as soon as he/she is able to sustain independent breathing. Identifying a patient's readiness for weaning and extubation can significantly reduce the overall duration of mechanical ventilation.
- The majority of adults are ready for extubation without weaning from mechanical ventilation.
- The spontaneous breathing trial is used widely across adult intensive care units to predict extubation readiness. Adults who tolerate SBTs for 30–120 min more often than not will be extubated success-

fully. Extubation success is defined as not requiring reinstitution of mechanical ventilator support for 24 or 48 h (MacIntyre 2001).

- The criteria to tolerate an SBT are usually multiple including physiologic parameters to define adequate gas exchange, respiratory pattern, hemodynamic stability, and signs or symptoms of distress.
- Like adults, many children can be successfully extubated without weaning from mechanical ventilation. Forty-one percent of children passed an “extubation readiness test” prior to starting a weaning mode (Randolph et al. 2002). Patients should be tested for extubation readiness as soon as they are able to wean.
- There are many indices used to predict extubation success. However, no one measure is consistently able to predict success.

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Anne Greenough and Andrew Currie

Educational Aims

- To describe efficacious respiratory support strategies pre and post extubation
- To facilitate an understanding of the physiology underlying predictors of weaning/extubation
- To highlight efficacious adjunctive therapies to hasten weaning and facilitate extubation

Bronchopulmonary dysplasia (BPD) has a multifactorial aetiology which includes prolonged use of mechanical ventilation. It is, therefore, desirable to wean, particularly prematurely born, infants from the ventilator as soon as possible. It is, however, equally important to neither undertake inappropriate weaning as this can result in an increased work of breathing nor extubate too

early as this may result in an acute deterioration and need for reintubation. In this section, the evidence for respiratory strategies pre and post extubation is reviewed and the efficacy of predictors of weaning and extubation success and adjunctive therapies discussed.

58.1 Ventilation Modes During Weaning from Mechanical Ventilation

58.1.1 Patient-Triggered Ventilation

Meta-analysis of randomised trials demonstrated that patient-triggered ventilation, delivered either as assist control ventilation (ACV) or synchronised intermittent mandatory ventilation (SIMV), compared to intermittent positive pressure ventilation was associated with a shorter duration of ventilation in infants recovering from respiratory distress (Greenough et al. 2012). In randomised trials, ACV compared to SIMV was associated with a shorter duration of weaning when the SIMV rate was reduced below 20 bpm (Dimitriou et al. 1995), likely reflecting that reducing the number of spontaneous breaths supported by mechanical breaths below a critical level increases the work of breathing. Indeed, the transdiaphragmatic pressure time product, which reflects the energy expenditure of the diaphragm muscle during isometric and non-isometric contractions, was significantly lower when prematurely born infants who were being weaned from

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the ventilator received pressure support and SIMV (i.e. all spontaneous breaths were supported) rather than SIMV alone (when only a proportion of the spontaneous breaths were supported) (Patel et al. 2009). Those results (Dimitriou et al. 1995; Patel et al. 2009) suggest that weaning is best achieved when all of the infant's spontaneous breaths are supported by positive pressure inflations.

58.1.2 Volume-Targeted Ventilation

During volume-targeted ventilation (VTV), a pre-set tidal volume is delivered despite changes in the infant's lung mechanics. Meta-analysis of the results of four randomised trials (McCallion et al. 2010) demonstrated VTV was associated with a significant reduction in the duration of ventilation. The trials, however, were of small sample size, including in total only 178 infants. In addition, different ventilator types were used which deliver different airway pressure waveforms during VTV (Sharma et al. 2007). Subsequent randomised trials have not demonstrated advantages of VTV with regard to facilitating extubation (Singh et al. 2006; Cheema et al. 2007).

58.1.3 Low Rate Intermittent Positive Airway Pressure

Infants may be extubated from low rate intermittent positive airway pressure versus extubation from a trial of endotracheal CPAP in intubated preterm infants (Davis and Henderson-Smart 2001). Three trials were identified but when RCTs only were considered, direct extubation from low rate ventilation rather than period of endotracheal CPAP was associated with a significantly greater extubation success (RR 0.10, 95 % CI 0.001, 0.78) (P). Twelve randomised studies have been included in a meta-analysis (Wheeler et al. 2010) and VTV modes were associated with a reduction in days of ventilation (−2.36 95 % CI −3.9 to −0.8) as well as reductions in death or BPD, pneumothorax and PVL or grade 3–4 IVH.

58.2 Assessing Readiness for Extubation

Interpretation of the literature is complicated by use of various definitions of extubation success which include remaining extubated at 24 h (Belani et al. 1980; Wilson et al. 1998), 48 h (Dimitriou et al. 2002; Fox et al. 1993; Kavvadia et al. 2000; Smith et al. 1999; Szymankiewicz et al. 2005; Vento et al. 2004) or 72 h (Dimitriou et al. 1999; Fox et al. 1981; Kamlin et al. 2008, 2006; Veness-Meehan et al. 1990). In addition, although most studies define extubation failure as the need for reintubation (Wilson et al. 1998; Dimitriou et al. 2002; Fox et al. 1993; Kavvadia et al. 2000; Szymankiewicz et al. 2005; Vento et al. 2004; Fox et al. 1981; Kamlin et al. 2008, 2006; Shoults et al. 1979; Balsan et al. 1990; Gillespie et al. 2003), others include a requirement for nasal continuous positive airways pressure (Belani et al. 1980; Veness-Meehan et al. 1990). Approximately 30 % of infants fail extubation when extubation readiness is determined by clinical criteria (Sinha and Donn 2000). Successful weaning and extubation are dependent on the balance between the magnitude of the respiratory load, the effective respiratory drive and adequate respiratory muscle strength. Assessment of the individual components has yielded variable success, including measures of compliance (Dimitriou et al. 2002; Kavvadia et al. 2000; Smith et al. 1999; Szymankiewicz et al. 2005; Veness-Meehan et al. 1990; Balsan et al. 1990) and resistance (Fox et al. 1981; Veness-Meehan et al. 1990). Lung volume assessment was shown to be significantly associated with extubation failure (Dimitriou et al. 1996) but post rather than pre-extubation and measurement of functional residual capacity using a helium gas dilution technique requires considerable expertise. A more generalisable technique is computer-assisted analysis of the chest radiograph lung area. A low post extubation lung area was demonstrated to be predictive of extubation failure but, although had a 100 % positive predictive value, had only 57 % sensitivity (Dimitriou and Greenough 2000). Respiratory drive has been assessed by the ventilatory

response to added dead space (tube breathing) but successful extubation was predicted with only 71 % sensitivity and 75 % specificity (Fox et al. 1993). Respiratory muscle strength has usually been determined by assessment of the maximum pressure generated during an occlusion ($P_{i_{max}}$). Although in some studies (Belani et al. 1980; Shoults et al. 1979) $P_{i_{max}}$ has been found to differ significantly between those in whom extubation failed and succeeded, differences in one study (Dimitriou et al. 2002) disappeared once $P_{i_{max}}$ was corrected for birthweight.

As a consequence, it seems likely that a better approach would be to determine the balance between the magnitude of the respiratory load, respiratory drive and respiratory muscle strength. This can be determined by the effectiveness of respiratory efforts, for example, the magnitude of minute volume. In one trial (Gillespie et al. 2003), infants randomised to extubation decided by a minute ventilation test rather than clinical judgement, were extubated significantly sooner (8 versus 36 h), but there were no significant differences in the extubation failure rate between the two groups. An alternative approach has been to measure the tension time index of the diaphragm (TTdi), which is calculated as the product of mean transdiaphragmatic pressure (P_{di}) and maximal P_{di} ($P_{di_{max}}$) and the ratio of inspiratory time (T_I) to the total respiratory cycle time (T_{TOT}) that is $TTdi = (P_{di}/P_{di_{max}}) \times (T_I/T_{TOT})$. Healthy human volunteers could not sustain a set breathing task for longer than 45 min when the TTdi was greater than 0.15 (Bellemare and Grassino 1982a, b). In addition, in patients with chronic obstructive airways disease, those failing weaning had a mean TTdi of 0.17 compared to 0.09 in those who were successfully weaned (Purro et al. 2000). In a paediatric intensive care population, a TTdi of greater than 0.15 was demonstrated to be 100 % sensitive and 100 % specific of extubation failure (Harikumar et al. 2006), retrospective analysis of neonatal data showed similar results (Currie et al. 2011). It is now important to prospectively investigate TTTdi and TTmus (a non invasive assessment of the force produced by the respiratory muscles) in a neonatal population.

58.3 Interventions That Might Facilitate Weaning from the Ventilator

58.3.1 Continuous Positive Airway Pressure and Nasally Delivered Ventilation Modes

Meta-analysis of eight trials demonstrated that nasal CPAP, when applied to infants being extubated following mechanical ventilation, significantly reduced (relative risk 0.62, 95 % CI 0.49, 0.77) the incidence of adverse clinical incidents (apnoea, respiratory acidosis and increased oxygen requirements) which indicated the need for additional respiratory support (Davis and Henderson-Smart 2009b). The efficacy of nasal CPAP, however, may depend on the delivery technique. Post extubation, in a randomised trial of 162 extremely low birthweight (ELBW) infants, CPAP delivered by the infant flow device rather than via a ventilator and nasal prongs was associated with a shorter requirement for supplementary oxygen, although not significantly greater extubation success (Stefanescu et al. 2003). There have, however, been concerns that use of dual nasal prongs may result in an increased risk of nasal trauma (Robertson et al. 1996), but subsequently similar incidences of trauma have been demonstrated regardless of CPAP mode delivery (Buettiker et al. 2004; Yong et al. 2005). The duration of CPAP, however, was noted to be significantly related to the occurrence of trauma (Yong et al. 2005). Hence, it is important to wean infants from CPAP as soon as possible. CPAP may be weaned by reducing pressure or by reducing the time spent on CPAP each day. In a randomised trial, weaning by pressure was shown to be associated with significantly more weaning success (Soe 2007).

Meta-analysis of randomised trials demonstrated that three nasal intermittent positive pressure ventilation (NIPPV) compared to CPAP increased successful extubation (relative risk 0.21, 95 % confidence intervals 0.10–0.45) (Davis et al. 2001). The studies, however, were of small sample size, and thus it is not possible to confidently conclude that nasal ventilatory modes do not increase gastrointestinal problems, as reported in earlier studies.

58.3.2 Pharmacological Interventions

58.3.2.1 Methylxanthines

Meta-analysis of six randomised trials demonstrated that methylxanthine treatment resulted in a significant reduction in failure of extubation within 1 week (relative risk 0.47); the number needed to treat to prevent one case of failed extubation was 3.7 (Henderson-Smart and Davis 2010). Methylxanthines were found to be most efficacious in infants with a birthweight of less than 1,000 g and a postnatal age of less than 7 days in age (Henderson-Smart and Davis 2010). Dosage may also be important. In 234 infants born at less than 30 weeks of gestation, high-dose (20 mg/kg) compared to low (5 mg/kg)-dose caffeine was associated with significantly less failure to extubate (15 % versus 30 %, $p < 0.01$) (Steer et al. 2004). There were no significant differences in major adverse effects, mortality or neurodisability at 1 year between the two groups, but those receiving the higher dose took a longer time to regain their birthweight (14.8 versus 12.9 days, $p < 0.01$) (Steer et al. 2004). In a large multicentre trial investigating caffeine therapy for apnoea (Schmidt et al. 2006) including infants of birthweight between 500 and 1,250 g, CPAP was discontinued 1 week earlier ($p < 0.001$) in those randomised in the first 10 days to caffeine rather than placebo; the “caffeine” infants also had a significantly lower incidence of BPD (36 % versus 47 %) and the only short-term adverse effect was a lower weight gain ($p < 0.001$). At 18–21 months of corrected age, fewer caffeine treated infants had survived with neurodevelopmental impairment (Schmidt et al. 2007). Seven studies have been included in the most recent meta-analysis of prophylactic methylxanthines for endotracheal extubation in prematurely born infants (Henderson-Smart and Davis 2010). Methylxanthine treatment resulted in reduction of failure of extubation with one week (RR 0.48 95 % CI 0.32 to 0.71).

58.3.2.1.1 Doxapram

Doxapram stimulates both peripheral and central chemoreceptors. Two randomised trials have been performed; no significant differences in failed extubation or duration of ventilation were shown. There was a trend for hypertension or irritability leading to cessation of treatment to be more com-

mon in infants treated with doxapram (RR 3.21, 0.53–19.43) (Henderson-Smart and Davis 2000); hence, this treatment is not recommended.

58.3.2.1.2 Corticosteroids

There have been numerous trials examining the efficacy of systemically administered corticosteroids with regard to reducing the duration of ventilation and BPD and these have been analysed according to the age at which the corticosteroids were given. Meta-analysis of 19 trials of corticosteroids given in the first 96 h (Halliday et al. 2010) demonstrated that significantly more infants were extubated both at 3 days (RR 0.74, 95 % CI 0.62, 0.78) and 28 days (RR 0.80, 95 % CI 0.67, 0.96). Similarly meta-analysis of the results of seven trials in which corticosteroids were given between 7 and 14 days demonstrated that extubation at 28 days was improved (RR 0.62, 95 % CI 0.51, 0.78) (Halliday et al. 2003) and nine trials in which corticosteroids were given after 21 days demonstrated that extubation at 28 days was significantly more common (RR 0.54, 95 % CI 0.32, 0.92) (Halliday et al. 2009). There are, however, concerns that systemically administered corticosteroids have undesirable side effects. As a consequence, the efficacy of low-dose dexamethasone (0.89 mg/kg over 10 days) has been compared to placebo in a randomised trial including infants born prior to 28 weeks gestation or whose birthweight was less than one kilo and were ventilator dependent after the first week after birth. Dexamethasone treatment was associated with more infants being successfully extubated by 10 days (60 % versus 12 %, $p < 0.01$) and a shorter duration of ventilation (14 versus 21 day, $p = 0.03$) (Doyle et al. 2006). No longer-term (Doyle et al. 2007) adverse effects were reported, but only 70 of the 814 planned sample size were recruited. An alternative approach to avoid the side effects of systemically administered corticosteroids is to give the steroids by inhalation. In nine trials, extubation success was increased in the infants treated with inhaled steroids administered for 1–4 weeks (RR 0.12, 95 % CI 0.03, 0.43) (Lister et al. 2000). Whether, differences in drug type, duration of therapy, delivery systems, co-interventions and disease severity influenced the results remains to be answered.

Corticosteroids are also given to reduce upper airway obstruction and hence facilitate extubation. Meta-analysis of three randomised trials

demonstrated that dexamethasone given prior to extubation significantly reduced the need for reintubation (Davis and Henderson-Smart 2009a), but side effects were reported. The authors (Davis and Henderson-Smart 2009a), therefore, concluded that intravenous dexamethasone should be restricted to infants at increased risk of airway oedema and obstruction.

58.4 Summary

Patient triggered (assist control ventilation ACV or synchronous intermittent mandatory ventilation SIMV) compared to conventional ventilation has been demonstrated in randomised trials to shorten the duration of ventilation in infants recovering from respiratory distress. ACV appears better than low rate SIMV. Studies are required to determine whether the newer patient-triggered ventilation modes are more efficacious as weaning modes than ACV. Assessments which assess the efficacy of respiratory efforts, the balance between respiratory drive, respiratory muscle performance and respiratory load seem likely to be most useful in predicting weaning and extubation success. Nasal CPAP post extubation reduces the need for reintubation in very prematurely born infants; further work is needed to assess the role of other nasally delivered ventilatory modes. Methylxanthines and corticosteroids increase extubation success; the side effects of systemically administered corticosteroids, however, preclude their routine use.

Essential to Remember

- Ventilation modes which support all the infants' spontaneous respiratory efforts are the more efficacious method of weaning.
- Assessments of the efficacy of respiratory efforts, that is the balance of respiratory drive, muscle performance and respiratory load, are most useful in predicting weaning and extubation success.
- Nasal CPAP reduces the need for reintubation in very prematurely born infants.
- Methylxanthines increase extubation success.

Future Perspectives

- Studies are required to determine whether pressure support or assist control ventilation is the more efficacious weaning mode.
- It is essential to determine if there is a corticosteroid regime with a positive risk-benefit ratio with regard to facilitation of extubation.
- The role of nasal ventilatory modes requires further investigation.

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Part XXIII

Automation of Mechanical Ventilation

Explicit Computerized Protocols for Mechanical Ventilation in Children and Neonates

59

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Educational Aims

With this chapter, the reader will be able:

- To describe the difference between a guideline, a written protocol, and an explicit computerized protocol
- To make the difference between an open-loop and closed-loop explicit protocol
- To list the major components of an explicit computerized protocol
- To give an example of a pediatric weaning explicit protocol on mechanical ventilation

In mechanical ventilation, the standardization of care with protocols improves patient outcomes. The more detailed the protocol is, the better the standardization of care is. Explicit computerized protocols (ECP) are made of a set of standardized orders, with detailed explicit instructions based on dynamic patient-specific parameters and available at the point-of-care. ECPs are usually developed in open loop where a recommendation is displayed and an active intervention by the clinician is required to apply this recommendation. After a validation phase, ECP can be implemented in closed loop, where ventilator settings are dynamically adjusted to a patient's condition according to the ECP recommendations without caregiver intervention. This chapter describes current knowledge in explicit computerized protocols in children.

59.1 Introduction

Pediatric and neonatal critical care has been practiced formally for over 50 years (Willson et al. 2006), and mechanical ventilation is one of the most common characteristic and dramatic intensive care unit procedures with about 30 % (range 20–60 %) of patients in a PICU supported by mechanical ventilation (Khemani et al. 2009). Mechanical ventilation in the Intensive Care Unit (ICU) is a life-saving method for those patients who cannot breathe on their own and it is administered until patients resume independent breathing (spontaneous breathing). Patients with acute

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respiratory distress syndrome (ARDS) and acute lung injury (ALI), in particular, typically require days or weeks of mechanical ventilation for respiratory failure. Despite our experience with mechanical ventilation, little is known about how best to ventilate patients with specific disease entities or syndromes such as ALI/ARDS. There is uncertainty about the best choice of ventilator type, mechanical ventilation mode, and the therapeutic goals of mechanical ventilation support (Randolph 2004) including best practices regarding weaning from mechanical ventilation, allowing resumption of spontaneous ventilation, and, finally, removing the endotracheal tube. However, there is no difference to the approach to mechanical ventilation over the pediatric age range under discussion (non-premature newborn to 18 years of age), with important values such as compliance of the respiratory system and tidal volume being indexed to weight to accommodate growth.

Pollack et al. (1987) reported that at a single-hospital, long-stay patients composed 7.1 % of the population but used 50.1 % of the PICU care days and 47.7 % of the technology resources and had a mortality rate of 17.4 % vs. 7.3 % for short-stay patients (Pollack et al. 1987). Long-stay patients are more likely to require respiratory support with an odds ratio of 6.48 (CI 95 % 5.26–7.98) (Marcin et al. 2001). On the other hand, respiratory support also increases the risk of complications attributable to the endotracheal tube, positive pressure ventilation, and/or sedation. In a prospective cohort study, Rivera and Tibballs (1992) reported complications in 24 % of 500 patients requiring respiratory support. Since respiratory support is required in the majority of children in PICU and because complications may occur with its use, it is essential to develop strategies to improve patient outcome and reduce medical errors related to mechanical ventilation.

59.1.1 Protocols, Impact on Healthcare

There is evidence that clinical decision making with protocol decreases practice variation between clinicians (Morris 2000), standardizes

patient care (Grimshaw and Russell 1993), and improves patient outcomes (Grimshaw and Russell 1993; Grimm et al. 1975; Wirtschafter et al. 1981; Safran et al. 1996; Garg et al. 2005). Written protocols developed to improve the management of respiratory support decreased ventilator days in adults when compared to usual physician orders (Kollef et al. 1997; Ely et al. 1996; Saura et al. 1996; Smyrniotis et al. 2002). Similar findings are observed in pediatrics (Schultz et al. 2001) and neonates (Hermeto et al. 2009). However, written protocols are dependent on caregiver availability, are not sufficiently explicit so they remain dependent on clinician judgment, and are difficult to transfer from one PICU or NICU to another Intensive Care Unit (Morris 2000).

59.1.2 Clinical Decision Support Systems

Clinical Decision Support Systems (clinical DSS) are proposed to create dynamic, patient-specific standing orders and can be transferred to other hospitals. Clinical DSS are “active knowledge systems which use two or more items of patient data to generate case-specific advice” (Wyatt and Spiegelhalter 1991). Clinical DSSs are typically designed to integrate a medical knowledge base, patient data, and an inference engine to generate case-specific advice. They are used to support clinical diagnosis and treatment plan process (computerized protocols). Such computerized protocols promote use of best practices and patient-specific standing orders.

59.1.3 Computerized Protocols

Computerized protocols vary in terms of how dynamic they are, the degree of specificity of their recommendations and the level of integration into workflow (Morris 2000). On one end of the spectrum, there exist non-explicit guidelines that consist of a set of static recommendations (Roumie et al. 2006). At the other end of the spectrum are computerized protocols that

function as a set of standardized orders, with detailed explicit instructions based on dynamic patient-specific parameters, available at the point-of-care. The latter type of protocol is called an “explicit computerized protocol” (ECP) (Phansalkar et al. 2008). ECPs are usually developed in open loop where a recommendation is displayed and an active intervention by the clinician is required to apply this recommendation. After a validation phase, some or all the ECP recommendations can be implemented in a closed-loop ECP, where ventilator settings are dynamically adjusted to a patient’s condition according to the ECP recommendations without caregiver intervention but still under caregiver supervision and within safety limits.

This chapter will describe current knowledge in explicit computerized protocols in children. Closed-loop systems controlling local tasks, which determine only what the immediate next ventilation setting will be, are described in another chapter (proportional adaptive ventilation, neurally adjusted ventilatory assist, adaptive support ventilation). These closed-loop systems differ from ECP because they do not include a plan aimed at controlling the time-course process, but this latter modality will probably be included in ECPs in the future.

59.2 Principles for Computerized Protocol Development

The development of an explicit computerized protocol (ECP) should comply with the following principles (Morris 1998).

59.2.1 Clinical Team

Such protocols are designed to be used by a large number of clinicians in different units with different organizations (see chapter on organization of mechanical ventilation). For protocols to be adapted to these various situations, the team in charge of the development should involve several clinicians from various disciplines (critical care physicians, respiratory therapists and nurses,

computer and biomedical engineers) with clinical credibility (team leadership). The panel of clinicians who are in charge of the development will have to build the ECP with the goal of saving clinician time in a busy environment along with providing safe decision assistance for the patients.

59.2.2 Explicit Variables and Rules

Computerized protocols should use quantifiable variables obtained from devices that monitor and support the patient. As mechanical ventilation necessitates and also produces many quantifiable variables (SpO_2 , End tidal and transcutaneous PCO_2 , blood gases, set and measured ventilation parameters, etc), it is the best area for which to develop such ECP. In a computerized protocol, some conditions have to be transformed by clinicians into a quantifiable variable. In other words, the variable “hemodynamic instability” must be defined by transformation into a quantifiable variable to avoid any difference in interpretation between caregivers, e.g., “dopamine $>5 \mu\text{g/kg/min}$ and/or any dose of epinephrine or norepinephrine.”

Clinicians may be able to enter data manually but these data should be unambiguous (i.e., any member of the caregiving team would enter the same data in the same circumstance). Data entered manually should be the exception in order to simplify the caregivers’ work. In the example of hemodynamic instability, data may be acquired directly from the patient’s infusion pump or the electronic medical record.

Explicit rules use either validated mathematical formula resulting from physiological studies (for example, alveolar gas equations (Otis et al. 1950)) or the formulation *if ... then ...* (for example, *if SpO_2 is below 92 % then increase FiO_2 by 0.1*). All potential paths that could be taken by the child during his or her PICU course should result in a specific instruction.

The clinician team in charge of the ECP develops variables, thresholds, and explicit rules according to current knowledge. In some cases, data may not exist to support decisions. Here, the team have to design observational or even clinical

trials to define some thresholds or explicit rules. For example, in the development of an explicit protocol on weaning, a survey using scenarios was conducted to validate the use of tidal volume, respiratory rate, and end-tidal CO₂ in children (Santschi et al. 2007; Jouvét et al. 2007).

59.2.3 Explicit Instructions

Similar to the definition of rules and thresholds, instructions must be unambiguous. In mechanical ventilation, most of the instructions will be the following: “setting unchanged”, “setting increased by x unit,” or “setting decreased by x unit.”

59.2.4 Application at the Point of Care

The instructions will be delivered at bedside computer terminals or even in the monitor or ventilator. ECP is usually developed in a manner that it can be used in “open loop” (the recommendation is displayed on a screen and the caregiver has the opportunity to accept or reject the recommendation). Ultimately, with refinement of protocols and with clinician acceptance of safety, the ECP can work in closed loop (recommendation is directly implemented without caregiver intervention). Specific data displays to explain the decision process are mandatory.

59.2.5 Representative Data

Data that are used to create instructions must be acquired in real time and validated before being processed to create an instruction. This necessitates the analysis and validation of input data using artifact detector, noise remover, and/or data smoothing. For example, to limit the effect of physiological variation in respiratory rate, the representative variable used for respiratory rate in an ECP could be the mean value over a specific time such as a 2-min interval (Jouvét et al. 2007).

59.2.6 Iterative Refinement

Iterative refinement of the rules during the development phase and even later is important to capture all specific reasons for clinician refusal to follow instructions, to analyze them, and to decide to modify or not to modify rules. It is the *sine qua non* condition to develop a robust ECP.

59.2.7 Simplicity

Simplicity in the rules and simplicity in the use of the application are essential. To ensure user acceptance, users must feel that they can count on the system to be available whenever they need it. The response time must be fast, data integrity must be maintained, and data redundancy minimized. It is the reason why systems have to be functioning at many sites for a period of time, so that major problems or software bugs have been eradicated, decreasing down time and improving acceptance. It is also important to assess the amount of training required for users to feel comfortable with the ECP. If users become frustrated with the ECP, as a consequence its performance will be suboptimal.

59.3 Basic Structure of an Explicit Computerized Protocol

The three components of an explicit computerized protocol are (1) data input (entered manually or captured electronically from devices), (2) a control unit that analyzes the input data to generate orders, and (3) data output (Fig. 59.1).

59.3.1 Input Data

The major issue is to select data that will be helpful and easily integrated into the ECP. Input data depends on the basic structure of the system, the mode of ventilation used, and the type of patients the system is designed for. Input data include.

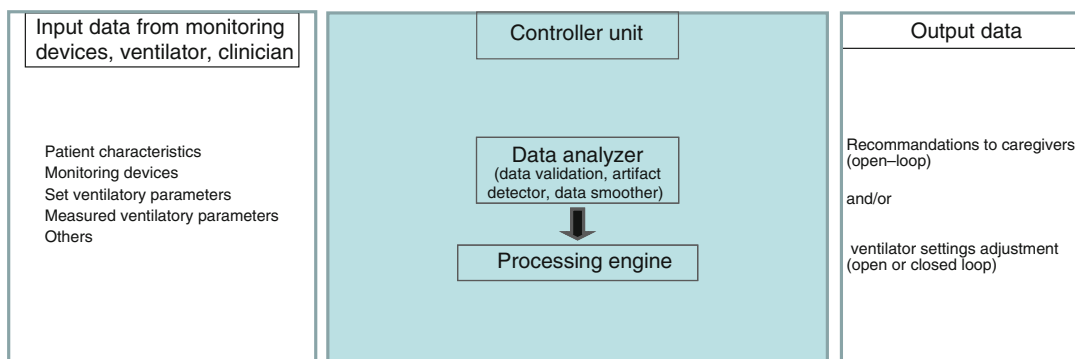


Fig. 59.1 The three components of an explicit computerized protocol

59.3.1.1 Patient Characteristics

The first parameter that needs to be defined is the child's lung volume. As we do not measure this volume, we need to use a surrogate that correlates with lung volume across ages, gender, and body habitus. Actual body weight is not accurate enough as children may be malnourished or have obesity. Height is a better surrogate in most of the cases except when neuromuscular weakness or spinal deformity is present. In such circumstances, ulna length is proposed (von Ungern-Sternberg et al. 2009; Gauld et al. 2003). Other characteristics include disease categories to identify patients with a specific breathing pattern (e.g., chronic obstructive pulmonary diseases) (Dojat et al. 2000), airway access (endotracheal tube, tracheostomy, facial mask), and humidifying system.

59.3.1.2 Ventilator Input Data

Ventilator input data may include set ventilatory parameters according to the ventilation mode (respiratory rate, tidal volume, PIP, PEEP, FiO₂, inspiratory/expiratory (I:E) ratio) and measured ventilatory parameters (spontaneous respiratory rate, expiratory tidal volume and/or air leak, dynamic compliance, resistance, etc).

59.3.1.3 Blood Gas Data

CO₂ removal is assessed by arterial or capillary PCO₂ on blood gas, ET_{PCO_2} , and transcutaneous PCO₂ and also indirectly by spontaneous

respiratory rate and tidal volume in some assist modes when respiratory control is functioning properly. Oxygenation is assessed by PaO₂ on blood gases, SpO₂, and transcutaneous PO₂. Blood gas analysis drives current ventilator management when ventilation is modified a few times a day. Blood gases cannot be used in an ECP where ventilation is adjusted in real time to patient's need. For real-time adjustment of ventilation, ECPs are currently using SpO₂ and/or ET_{PCO_2} in addition to respiratory rate and tidal volume (Jouvet et al. 2007).

59.3.1.4 Hemodynamic Data

The heart is a pump within a pump (thoracic cage). Any modification of the ventilation pump may impair the cardiac pump. It is necessary to include in ECPs variables that define and/or monitor hemodynamic status. The simplest variable proposed is to ask caregivers if there is hemodynamic instability, but this assessment is not explicit enough. Plethysmographic wave analysis displayed by pulse oximeters may be used as a quantifiable variable of hemodynamic stability (Frey et al. 2008). Further research on this topic is mandatory to develop an accurate marker of hemodynamic status during mechanical ventilation. The Shock Index (systolic blood pressure divided by the heart rate) may be useful in the future, along with input on inotrope and/or vasopressor infusions from the electronic medical record or the infusion pump, as mentioned earlier.

59.3.2 Control Unit

The control unit is a computerized unit that receives clinical information on the patient (input data) and transforms this information into orders (output data). It is comprised of several systems:

- The first system transforms the input data into validated data to limit measurement artifacts and transient variation in the patient's condition. Such systems use data smoothing and temporal abstraction techniques to exclude artifacts and noise. This step is already partially done by many medical devices used in clinical practice, such as pulse oximeters and cardio-monitors. For example, the weaning ECP for children (Smartcare/PS®, Dräger, Germany) transforms real-time tidal volume, respiratory rate, and ET_{PCO_2} into mean values over a 2-min period. These mean values are used to generate orders (Jouvet et al. 2007). For CO_2 removal parameters, a mean value every 2 min seems adequate. For oxygenation 2 min is too long, and we are currently working on a system that integrates mean SpO_2 over a 1-minute period.
- After validation, the data and their evolution with time are processed to generate orders. The basic structure of the information processing is rule-based. The rules use either validated mathematical formula (physiological model) or the formulation *if ... then ...* (Tehrani and Roum 2008). Some ECPs were developed with fuzzy logic, but they were not readily accepted for clinical trials, possibly due to the lack of visibility on how the internal decision process is conducted (Olliver et al. 2003). To generate orders with the formulation *if ... then ...*, thresholds for each variable must be defined. For example, “*if tidal volume is below 6 ml/kg, then increase positive inspiratory pressure by 2 cmH₂O.*” All potential paths that could be taken should result in a specific instruction. This requires either the number of input variables to be limited or the need to create several small sets of rules that manage 2–3 input data each. For example, a first set of rules is managing pressure support level according to tidal volume, respiratory rate, and ET_{PCO_2} (Jouvet et al. 2007), and a second set of rules is managing FiO_2 and PEEP according to SpO_2 (Lellouche et al. 2009). Another

set of rules will recommend extubation when pressure support level, PEEP, and FiO_2 reached a threshold for a given period of time that corresponds to an extubation readiness test (Jouvet et al. 2007).

59.3.3 Output Data

Output data can be either recommendations to the caregivers suggesting new ventilator settings, specific orders such as “patient ready for separation from the ventilator,” or ventilator settings being automatically adjusted by a “feedback control.” During the development phase of an ECP, output data are usually recommendations that the caregiver have to set. After extensive testing some rules or sets of rules can be switched to a “closed-loop” system, i.e., implementation of the recommendation without caregiver intervention.

A simple, attractively presented and intuitive user interface is crucial to facilitate the understanding of the ECP decision process and for knowledge transfer at the bedside (Wysocki and Brunner 2007). Ideally, the user interface should include education tools with which to train caregivers on mechanical ventilation management according to the ECP, as is done with simulators for aircraft pilots.

59.4 Example of an Explicit Computerized Protocols: Smartcare/PS®

The Smartcare/PS® ECP was first elaborated for adults and was based on the representation in a computer of knowledge of experienced intensivists. This ECP focuses on the management of pressure support ventilation, with or without a positive end-expiratory pressure. The knowledge corpus comes essentially from the scientific literature and from a group of intensivists, physiologists, and scientists at Henri Mondor hospital (Créteil, France) (Dojat et al. 2000; Dojat and Brochard 2001). This ECP interprets clinical data in real time and controls the mechanical assistance provided to mechanically ventilated patients. This ECP increased or

decreased pressure support level (a surrogate of CO_2 removal) and was adapted to children. Smartcare/PS[®] ECP develops a therapeutic strategy that gradually reduces the level of assistance, at a pace depending on the patient’s tolerance, and evaluates his/her capacity to breathe without mechanical assistance. The ECP uses three main parameters acquired from the patient by the ventilator: respiratory rate (RR), tidal volume (V_t), and end-tidal partial pressure of CO_2 (ET_{PCO_2}) (Fig. 59.2). It controls the level of

pressure above PEEP during ventilation in the pressure support mode according to V_t , RR, and ET_{PCO_2} and has two main functions: (1) automatic adaptation of the mechanical ventilation assistance to maintain the patient in a normal breathing zone and (2) weaning strategy (Jouvet et al. 2007). An example of breathing pattern with Smartcare/PS[®] is shown in Fig. 59.3. Smartcare/PS[®] does not manage oxygenation parameters and does not support younger children, currently.

Input data	Controller module	Output data
– Body weight – Humidifying system – Ventilation mode – ET leakage – V_t – RR – ET_{PCO_2}	– <i>Data analyzer:</i> V_t, RR, ET_{PCO_2} mean values on 2 min – <i>Engine</i> with more than 100 rules (<i>if ... , then ...</i>) – <i>User interface</i> incorporated in the ventilator	– PS level adjustment – Recommendation: “separation from the ventilator”

Fig. 59.2 Characteristics of the components of Smartcare/PS[®] explicit computerized protocol. ET endotracheal tube, V_t tidal volume, RR respiratory rate, ET_{PCO_2} end-tidal PCO_2

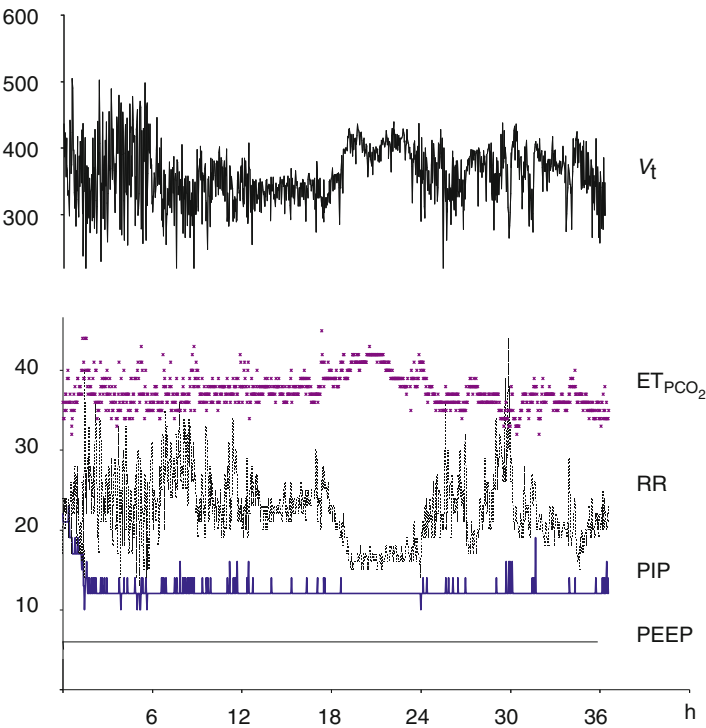


Fig. 59.3 Example of the parameters monitored by Smartcare/PS[®] and resulted modifications of pressure support level (PIP) in a 17-year-old adolescent during the weaning phase of an ARDS. We observed a dramatic decrease in the PS level the first 2 h after initiation of the explicit computerized protocol. The mean number a PS level changes over 36 h was 5 changes per hour

59.5 Clinical Evaluation of Explicit Computerized Protocols

59.5.1 Explicit Computerized Protocols for Respiratory Support in Adults

Explicit computerized protocols have been studied in adults in multicenter trials as treatment modalities for the acute respiratory distress syndrome (ARDS) (East et al. 1999) and for weaning (Lellouche et al. 2006). In all instances, a similar or better outcome was found when compared to usual care or to written protocol. East et al. (1999) included 200 patients with ARDS in a multicenter randomized trial. They observed a significant reduction in morbidity as measured by a multiorgan dysfunction score and a lower incidence and severity of lung injury. Lellouche et al. (2006) enrolled 144 patients in a European RCT and showed that weaning duration was reduced in the explicit computerized protocol group (SmartCare/PS®, Dräger, Germany) from a median of 5–3 days ($p=0.01$). This benefit was attributed to better compliance (94 % adhered fully), consistent orders that suppress interpretation variability among caregivers, and reduction of time lags between assessment of patient status and order and between order and execution. In Australia, a similar RCT did not observe any difference in weaning duration when SmartCare/PS® system was compared to weaning managed by experienced critical care specialty nurses, using a 1:1 nurse-to-patient ratio (Rose et al. 2008). This suggests that ECP impact may be influenced by the local clinical organizational context. A North American pilot RCT is currently in process (Burns et al. 2009).

59.5.2 Explicit Computerized Protocols for Respiratory Support in Pediatrics

In a pilot study with a before-and-after design (20 patients in each group), a 24 % decrease in the total duration of mechanical ventilation was observed between the control group (written

protocol) and the ECP group (Smartcare/PS®) (mean $\pm$ SD: 6.7 ± 11.5 days and 5.1 ± 4.2 days), but the difference was not statistically significant ($p=0.33$) (Jouvet et al. 2007). In a recent single-center randomized clinical trial comparing the same weaning ECP to usual care, at Sainte Justine Hospital in Montreal, weaning ventilation duration was dramatically decreased in the ECP group when compared to the control group, 36.4 ± 36.3 h ($n=15$) and 89.1 ± 119.9 h ($n=15$), respectively ($p=0.007$) (Jouvet et al. 2009).

In children and adults, standardization of oxygenation management involves PEEP/FiO₂ grids (International Consensus Conferences in Intensive Care Medicine 1999; Curley et al. 2006). Such PEEP/FiO₂ scales have been used as written guidelines in several clinical trials in pediatric intensive care including the prone positioning trial (Curley et al. 2005) and ongoing multicenter calfactant study for direct acute respiratory distress syndrome (CARDS trial) conducted by Willson et al. No explicit computerized protocol includes oxygenation management at this time for children outside neonates, but both authors of this chapter are working on such a controller for use in pediatric clinical trials.

59.5.3 Explicit Computerized Protocol for Respiratory Support in Neonatology

Claure et al. (2001) developed an SpO₂-FiO₂ closed-loop system to limit periods of hypo- and hyperoxemia. These authors demonstrated that in premature infants, their explicit protocol was at least as effective as a fully dedicated nurse in maintaining SpO₂ within the target range. Urschitz and coworkers (2004) performed a randomized, controlled, crossover clinical trial in 12 preterm infants with a similar computerized protocol. Periods with automatic and routine manual oxygen control were compared with periods of optimal control by a fully dedicated person. The median percentage of time with oxygen saturation levels within target range was 81.7 % for routine manual oxygen control and 90.5 % for

automatic control. These closed-loop systems could be incorporated into an ECP aimed at decreasing ventilation duration.

59.6 Challenges When Implementing an Explicit Computerized Protocol

Barriers to protocol use are huge including lack of awareness, lack of familiarity with the protocol, lack of agreement, lack of efficacy, lack of known improved outcome, and lack of ability to overcome the inertia of previous practice. There are also external barriers: (1) protocol-related barriers (not easy to use, not convenient, cumbersome, confusing) and (2) environment-related barriers (new resources or facilities not accessible) (Cabana et al. 1999). To ensure acceptance, users must feel that they can count on the system to be available whenever they need it. The amount of downtime needed for data backup, troubleshooting, and upgrading should be minimal. The response time must be fast, data integrity must be maintained, and data redundancy minimized. If systems have been functioning at other sites for a period of time, major problems or software bugs may have been eradicated, decreasing downtime and improving acceptance. It is also important to assess the amount of training necessary for users to feel comfortable with the system.

The ventilator market is also a barrier to the implementation of ECPs. There are numerous companies, and the competition between companies result in difficulties to implement the same ECP in different ventilators. On the other hand, for technical and regulatory issues, companies need to be involved in the process of implementation of ECPs on mechanical ventilation. Ventilators dedicated to pediatric and neonatal intensive care are a small market when compared to the adult one. What pediatric and neonatal intensivists need to develop are ventilation ECPs that can be adapted afterwards by the different companies into the type of ventilator they sell. This can be done either by developing an ECP in a ventilation mode widely used (e.g., pressure

support mode for a weaning ECP) or by adaptation of the rules of the primary ECP to different modes (e.g., a weaning ECP in pressure support mode by Dräger Medical, in NAVA mode by Maquet, and in ASV mode by Hamilton) with a validation phase by a panel of pediatric and/or neonatal intensivists who were involved in the development of the primary ECP.

Conclusion

Despite the proven effect of decision support tools, there is no uniformity or agreement on ventilator management decisions. This results in a high variability in practice between centers and between intensivists at the same center (Santschi et al. 2010; Payen et al. 2009). Management of mechanical ventilation is an example of an iterative treatment protocol encompassing the many individual decisions that must be made over the course of a patient's treatment (Niland et al. 2006).

Decision support tools (paper or electronic) have been shown to improve the quality of medical care (Shortliffe and Cimen 2006), reduce errors (Slonim and Pollack 2005), and improve patient outcomes (Blaser et al. 2007). However, paper-based tools can be difficult to follow accurately, leading to low adherence rates (30 % compliance in a pediatric ventilator study with a paper protocol (Randolph et al. 2002) compared with 94 % in adult ventilator management studies with a computer-based protocol (Lellouche et al. 2006; Morris et al. 1994)). Computers can assist clinicians by standardizing descriptors and procedures, by consistently performing calculations, by incorporating complex rules with patient data, and by capturing data relevant to decision making (Niland et al. 2006; Clemmer 2004; Morris 2003; Morris et al. 1996). Computer-based protocols can contain extensive details, while at the same time protecting the user from complexity and information overload (Clemmer 2004; Morris 2003; Morris et al. 1996). These tools aim to ensure flexible but consistent, evidence-based clinician decisions for equivalent patient states.

Informatics is irresistible and irreversible. We are at the first stages in the development of ECPs in children and neonates. An ECP is only as effective as its underlying knowledge base, which changes as medical science evolves. The next generation of clinical decision support systems should be not only evidence based but also “evidence adaptive” with automated and continuous updating to reflect the most recent advances in clinical science and local practice knowledge (Sim et al. 2001). Flexibility in incorporating information from diverse sources and adaptability to varied practice settings are likely to be the quality criteria by which decision support systems will be judged in the future.

Essential to Remember

- There is no uniformity or agreement on ventilator management decisions nowadays. This results in a high variability in practice between centers and between intensivists at the same center.
- Explicit computerized protocols function as a set of standardized orders, with detailed instructions based on dynamic patient-specific parameters, available at the point-of-care.
- Explicit computerized protocols are only as effective as its underlying knowledge base.

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Educational Aims

- Describe the basic concepts and rationale behind the development of automatic FiO_2 controllers in premature infants.
- Present and discuss the findings from existing studies on automatic FiO_2 control.
- Discuss existing and possible limitations of automatic FiO_2 control.

60.1 Rationale and Methods

Supplemental oxygen is given to a large proportion of preterm infants to maintain adequate levels of oxygenation. In this population exposure to supplemental oxygen increases the risk of retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and oxygen radical injury to other organs and systems (McColm and Fleck 2001; Tin and Gupta 2007; Saugstad 2003). These effects are more pronounced in infants born at earlier gestational ages due to their immaturity and the prolonged duration of the exposure to oxygen.

Close monitoring of arterial oxygen saturation by pulse oximetry (SpO_2) is essential in all infants receiving supplemental oxygen to reduce the complications associated with excessive or insufficient oxygenation. Despite this, observational data indicate preterm infants spend only half of the time within the intended range of SpO_2 , nearly a third of the time with SpO_2 above, and one fifth of the time with SpO_2 below the intended range (Hagadorn et al. 2006; Laptook et al. 2006). Most of these infants show frequent fluctuations in oxygenation which is in part responsible for the time they spend with SpO_2 outside the intended range. This is compounded by the fact that during routine neonatal care, SpO_2 alarms are often improperly set or ignored (Clucas et al. 2007; Nghiem et al. 2008).

Caregivers often increase the fraction of inspired oxygen (FiO_2) or delay its weaning in an attempt to reduce the frequency or attenuate the severity of episodes of hypoxemia. Under ideal conditions, a fully dedicated caregiver could better maintain SpO_2 within the intended range, but this would impose significant demands on effort and time. Therefore, automated adjustment of inspired oxygen appears to be a good alternative to achieve the needed balance between adequate oxygenation, reduced exposure to supplemental oxygen, and availability of staff. In brief, systems for automatic adjustment of FiO_2 consist of continuous measurements of oxygenation and programmed adjustments to the inspired oxygen

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aimed at maintaining a set point or range of oxygenation. With these systems, when oxygenation declines below the set point or range, FiO_2 is increased automatically and vice versa.

Several systems for automated adjustment of FiO_2 have been developed and tested in infants receiving supplemental oxygen via mechanical ventilator, CPAP, or head-hood. These systems have utilized different methods of oxygenation monitoring with pulse oximetry being the most common. Although the primary aim of these systems is to maintain oxygenation within a target range or at a specific level, they differ in the algorithm directing the changes in FiO_2 . Some algorithms were designed to respond to gradual changes in oxygenation, while others were designed to respond to rapid fluctuations in oxygenation or both. In addition, some of these algorithms try to minimize the concentration of inspired oxygen as one of their objectives.

The feasibility and efficacy of automated FiO_2 adjustment in preterm infants have been documented in several studies (Beddis et al. 1979; Dugdale et al. 1988; Bhutani et al. 1992; Morozoff and Evans 1992; Sun et al. 1997; Claire et al. 2001; Urschitz et al. 2004; Claire et al. 2009; Bucher et al. 1994). In these trials techniques for automatic FiO_2 adjustment were utilized in neonates receiving various forms of respiratory support and with oxygenation monitored by different methods. Continuous oxygenation monitoring has been done by indwelling PaO_2 electrodes, transcutaneous PO_2 electrodes (TcPO_2), or SpO_2 measurements by pulse oximetry. Indwelling electrodes require the availability of an invasive catheter in place. During neonatal care invasive catheters are placed only on a per need basis, and for the most part they are removed as soon as these are no longer needed to avoid complications. TcPO_2 is a noninvasive technique but requires heating of the skin and frequent changes in site of application to avoid thermal injury and frequent calibration. In contrast, SpO_2 provides continuous information on oxygenation and it has become a standard of care for infants receiving supplemental oxygen.

60.2 Effects on Oxygenation and Oxygen Exposure

The studies of feasibility and efficacy consistently reported increased time spent within the target range of oxygenation during automated FiO_2 adjustment compared to routine care. Studies where automated FiO_2 adjustment was compared to a fully dedicated caregiver showed that the automated mode maintained oxygenation within the target range similarly or better than the dedicated caregiver.

The efficacy and beneficial effects of automated FiO_2 adjustment are largely relative to the type of care against which it is compared and to the type of fluctuations the infants present with. This is not only related to the effort of the caregiver but also to the actual SpO_2 range that is being aimed for during manual FiO_2 control. Infants who present with frequent episodes of hypoxemia represent a challenge not only to the caregiver but also to the automatic systems. In these infants, routine caregivers often tolerate high SpO_2 levels expecting that this will attenuate the frequency or severity of these episodes. In such cases, the reduction in hyperoxemia and supplemental oxygen by automated FiO_2 adjustment is more striking (Claire et al. 2009). The increased time with SpO_2 within a target range during automated FiO_2 adjustment compared to routine care was largely achieved by a striking reduction in time spent with high SpO_2 levels and was accompanied by exposure to lower levels of FiO_2 as shown in Fig. 60.1. The gradual reduction in the basal FiO_2 level and avoidance of high SpO_2 during automated FiO_2 adjustment are illustrated in Fig. 60.2.

The experiences with automated FiO_2 adjustment also reveal potential respiratory effects of targeting different ranges of SpO_2 . A lower targeted range of SpO_2 may reduce the infant's oxygen reserves and lead to an increased susceptibility to hypoxemia spells from small fluctuations in ventilation that would otherwise cause minimal effects on arterial oxygen content.

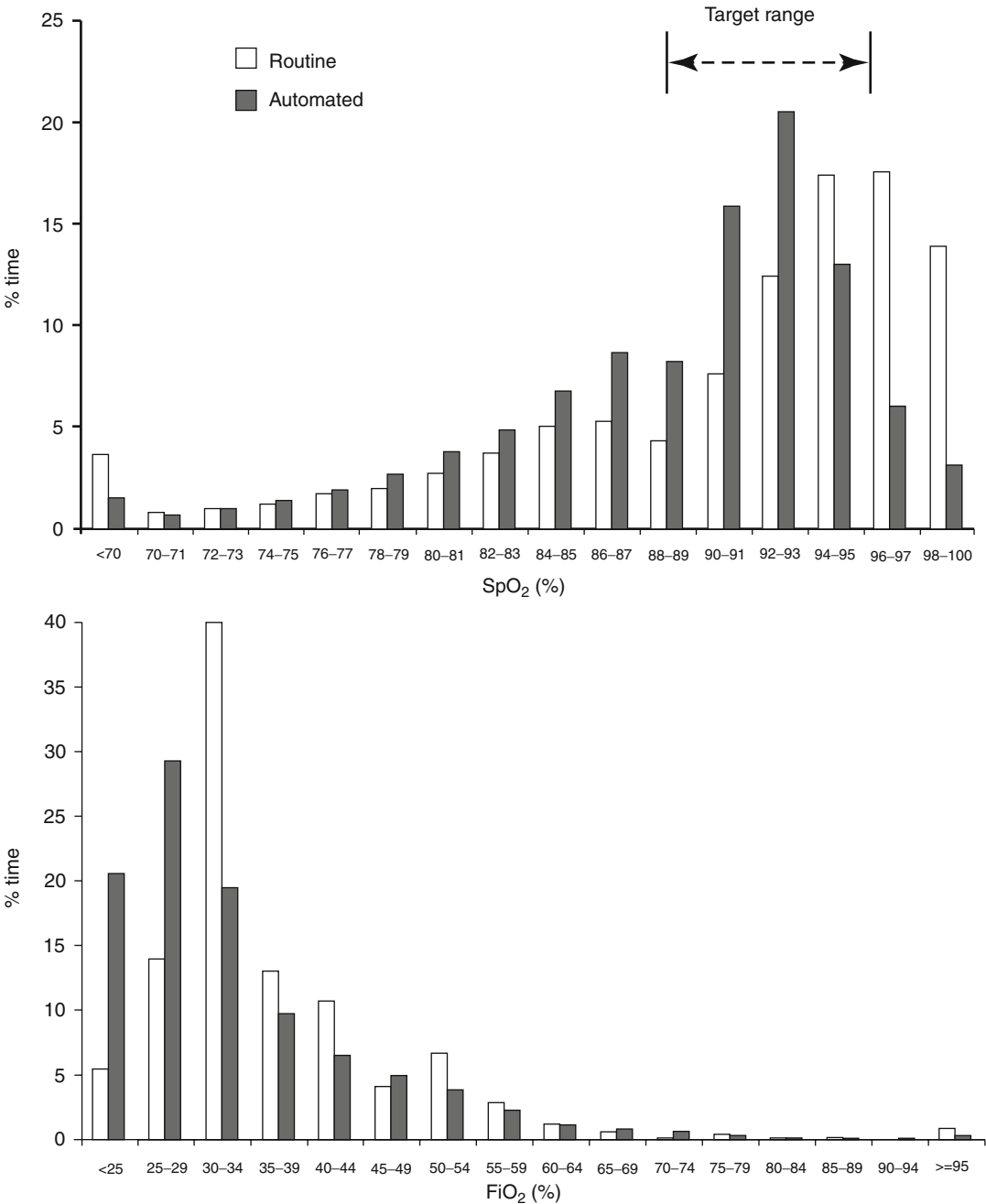


Fig. 60.1 Histograms of SpO₂ and FiO₂ show increased time within the target range of SpO₂ and a striking reduction in time spent with high SpO₂ during automated FiO₂ adjustment compared to routine care. This is associated with exposure to lower FiO₂ levels (Reproduced from [Claire et al. \(2009\)](#) with permission from *Journal of Pediatrics*)

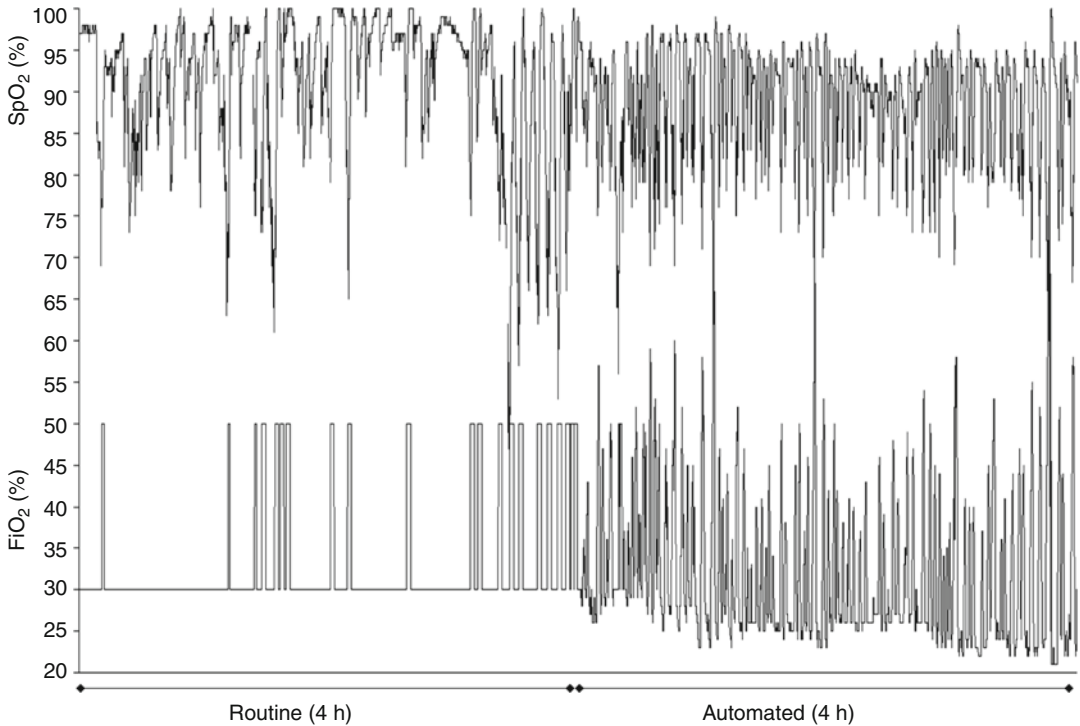


Fig. 60.2 Recordings of SpO_2 and FiO_2 during routine care show the caregiver response to episodes of hypoxemia. These are frequently followed by periods of hyperoxemia due to a persistently increased FiO_2 . In contrast, during the automated period there is a gradual reduction

in the basal FiO_2 which reduces hyperoxemia. However, this is accompanied by more frequent but relatively milder episodes of hypoxemia (Reproduced from Claure et al. (2009) with permission from *Journal of Pediatrics*)

60.3 Effects on Staff Workload

Data obtained in the studies evaluating automatic adjustment of FiO_2 have also illustrated the effort required to maintain oxygenation within the intended range. As expected, the number of FiO_2 adjustments by a dedicated caregiver was greater than those made by the routine caregivers and was also more effective in maintaining oxygenation within the intended range (Bhutani et al. 1992; Urschitz et al. 2004).

The effort spent in maintaining SpO_2 within an intended range also depends on the frequency of fluctuations. As expected, those studies involving infants with frequent episodes of hypoxemia documented more frequent manual FiO_2 adjustments. During routine care the caregiver must also be attentive to wean FiO_2 to the basal level after a hypoxemia spell has resolved to avoid

rebound hyperoxemia. This is commonly not done consistently and soon enough during routine care. This is illustrated in Fig. 60.2 where a routine caregiver was more attentive to intervene during episodes of hypoxemia than to prevent hyperoxemia. The gradual reduction in basal FiO_2 during the automated period is accompanied by more frequent but milder episodes of hypoxemia.

60.4 Limitations

Continuous and accurate availability of the infant's oxygenation is key in achieving an effective and safe automated adjustment of FiO_2 . The accuracy of pulse oximetry, the most commonly method used for automated FiO_2 adjustment, can be affected by motion artifact. Poor accuracy can

result in unnecessary exposure to supplemental oxygen levels during periods of falsely low SpO₂ or prolonged hypoxemia if this goes undetected. These risks are present during routine care as well as during automated FiO₂ adjustment. Other factors such as poor perfusion or inadequate probe placement and function can also reduce accuracy (Bucher et al. 1994). In general, conditions that impair SpO₂ reliability and make its use questionable during routine care for an individual infant should also be considered as contraindications for its use for automated FiO₂ adjustment.

The reliability of pulse oximetry in correctly identifying hypoxemia is important in automated FiO₂ adjustment. Although most reports indicate reliable detection of hypoxemia by new pulse oximeters (Bohnhorst et al. 2000; Hay et al. 2002), some hypoxemia alarms during periods of infant activity are considered false due to the possibility of movement artifact. However, true hypoxemia spells can be associated with or result from the infant's activity. These spells have been linked to increased activity and are more frequent when infants are awake (Bolivar et al. 1995; Esquer et al. 2007; Dimaguila et al. 1997; Lehtonen et al. 2002). This is important because artifactual hypoxemia spells during automated FiO₂ adjustment can result in unnecessary oxygen exposure. Reassuringly, in infants with frequent hypoxemia spells, automatic FiO₂ adjustment resulted only in minimal hyperoxemia overshoot (Claure et al. 2001, 2009). One would expect a high rate of hyperoxemia overshoot if most of the hypoxemia episodes were due to artifact.

Reduced attentiveness and poor observation of respiratory status may be an unwanted consequence of automated FiO₂ adjustment. In some instances additional oxygen may only provide palliative support while not addressing the root cause of hypoxemia such as hypoventilation. To avoid this, automated systems must warn the caregiver when the automatically set FiO₂ remains consistently elevated to maintain oxygenation in the desired range. Although this can be a potential drawback, it can be argued that the automatic increase in FiO₂ is a necessary first step to maintain the infant properly oxygenated

and reduce exposure to prolonged hypoxemia if the clinical intervention is delayed. Another important issue is the acceptance and adaptability of this form of automated support to the busy clinical environment of a newborn intensive care unit. This has been recently assessed under routine clinical conditions over 24-h periods without any adverse events (Claure et al. 2011).

The optimal range of oxygenation for preterm infants has not been determined. Exposure to high oxygenation levels has been shown to worsen respiratory and visual outcome with minimal or no beneficial effects. Observational studies where lower target ranges were used to avoid the effects of extremely high SpO₂ suggested improved outcome (Tin et al. 2001; Chow et al. 2003; Wright et al. 2006; Vanderveen et al. 2006), but it is unknown how well those ranges were maintained and is possible the actual SpO₂ may have exceeded those ranges. More recently, important evidence from a large trial indicated increased mortality with a lower SpO₂ target range (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network et al. 2010). Because automatic FiO₂ controllers will target a range set by the clinician, it is recommended that selection of the target range be done with caution and considering the possible physiologic effects of a more effective maintenance of a desired target range of SpO₂ by the automatic FiO₂ controller.

In summary, automated adjustment of FiO₂ can improve maintenance of oxygenation within the intended range, reduce hyperoxemia and supplemental oxygen, and reduce staff workload. Larger clinical randomized trials are necessary to determine the effects of this automated form of support on survival and long-term respiratory, ophthalmic, and developmental outcome.

Essentials to Remember

- Data indicate automatic FiO₂ control can improve maintenance of oxygenation within the intended range while reducing hyperoxemia, supplemental oxygen, and

workload compared to conventional manual adjustment of FiO₂.

- Automatic FiO₂ controllers are designed to maintain the target range of oxygenation determined by the clinician.
- Although at present time the optimal range of oxygenation for preterm infants has not been yet determined, evidence from recent and ongoing clinical trials should be used as guidance in the decision to select a target range of oxygenation.
- The effects of this automatic FiO₂ control on survival and long-term respiratory, ophthalmic, and developmental outcome are still to be determined.

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Educational Aims

With this chapter, the reader will be able:

- To describe the principles used in the modification of ventilator parameters by SmartCare/PS®
- To describe the principles used in the modification of ventilator parameters by IntelliVent®
- To describe the current clinical knowledge of these two automated modes for mechanically ventilated children

This chapter describes the basics and the clinical experience with two explicit computerised protocols (ECP) implemented in commercialised ventilators: Smartcare/PS® by Draeger Medical (Germany) and IntelliVent® by Hamilton

Medical (Switzerland). These two ECPs manage ventilation, without the need of caregivers' intervention but under their supervision. SmartCare/PS® is an autopiloting, knowledge-based software application that provides an ECP for the automated control of pressure support ventilation. IntelliVent® is an explicit computerised protocol for the automated control of minute volume, PEEP and FiO₂ in adaptive support ventilation (ASV). The main innovation of the two ECPs is the use of ET_{PCO₂} as a surrogate for blood gas PCO₂, to decrease or increase ventilatory support. IntelliVent® also uses SpO₂ to decrease or increase PEEP and FiO₂. The two ECPs were studied in children during the weaning phase and the first clinical studies are promising. However, further clinical trials are needed to better assess the efficacy and tolerance of these two ECPs in children and to develop ECP that are dedicated to all ages including neonates.

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61.1 Introduction

Discontinuing mechanical ventilation as soon as it is no longer needed is crucial in preventing respiratory and prolonged sedation complications. The weaning process is described in a previous chapter (see section on weaning Part XXII) and can be summarised in six steps according to the sixth international consensus conference on intensive care medicine (Boles et al. 2007) including (1) suspicion that weaning may be possible, (2) assessment of readiness to

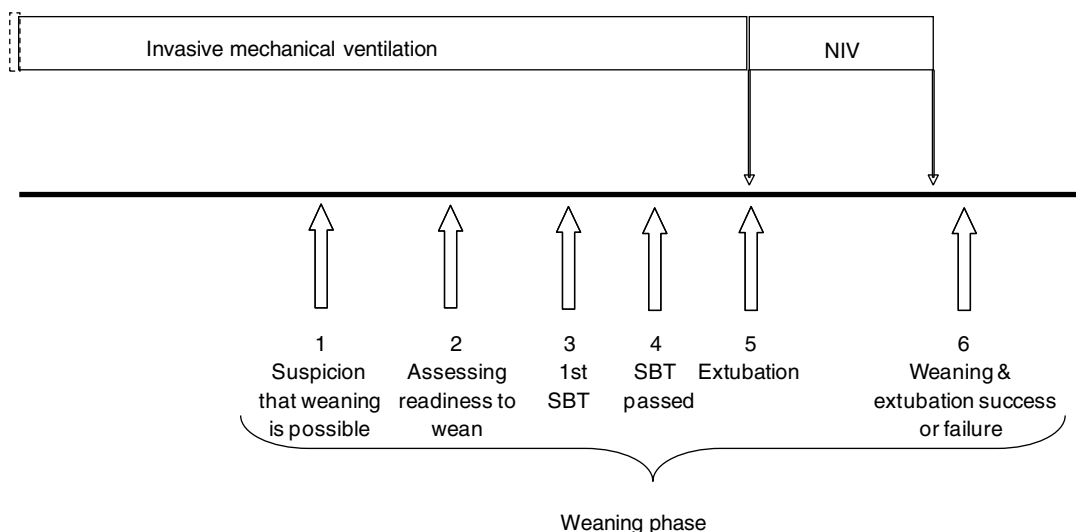


Fig. 61.1 Schematic representation of the different steps during weaning from mechanical ventilation in children

wean, (3) spontaneous breathing trial (SBT) performed, (4) SBT passed, (5) extubation and (6) assessment of successful or failure of extubation (Fig. 61.1). Between each steps mechanical ventilation has to be adapted to reach the next step until no ventilator support is needed anymore. At present, two explicit computerised protocols on weaning children from mechanical ventilation are implemented in commercialised ventilators. This chapter describes these two explicit computerised protocols: Smartcare/PS® by Draeger Medical (Germany) and IntelliVent® by Hamilton Medical (Switzerland).

61.2 SmartCare/PS®: Draeger Medical

SmartCare/PS®—PS stands for pressure support—is an autopiloting, knowledge-based software application that provides an ECP for the automated control of pressure support ventilation. This ECP manages, without the need of caregivers intervention but under their supervision, the four following therapeutic procedures: (1) automatic adaptation of the pressure support level to keep the patient inside a “zone of respiratory comfort”, i.e. normal ventilation (see below); (2) a strategy to gradually and progressively decrease the level

of pressure support level; (3) an automated SBT when the patient reaches a minimum ventilatory support; and (4) a recommendation of separation from the ventilator when the SBT is successfully passed (Table 61.1).

SmartCare/PS® is available on Draeger’s Evita XL and the latest generation of Draeger Medical ventilators: Evita Infinity V500. It is applicable in two applications that slightly differ: (a) for patients with ideal body weight (IBW) between 15 kg and 35 kg as well as for (b) patients with IBW between 36 kg and 200 kg. The ECP comprises of the three different phases “adaptation”, “observation” and “maintain” to perform ventilation procedures (1) to (4). It will also manage patient instabilities, e.g. transient tachypnoea, and it can cope with certain patient care situations like suctioning and pauses during specialised therapeutic situations like nebulisations or during specific ventilator alarm.

61.2.1 Basics of SmartCare/PS®

61.2.1.1 Initiation of SmartCare/PS®

Initiating SmartCare/PS® is recommended when a child, with IBW greater than 15 kg, fulfils ready-to-wean criteria that were used in two prospective clinical studies (Jouvet et al. 2007;

Table 61.1 Characteristics of the SmartCare/PS® Draeger Medical and IntelliVent® Hamilton Medical explicit computerised protocols

Characteristics	SmartCare/PS®	IntelliVent®
Mode of ventilation	PS	ASV
Body weight range for use (kg)	≥15	≥7
Weaning steps managed (see Fig. 61.1)	2–4	1–4
Primary goal of the ECP	Wean patient while maintained in normal ventilation (see Table 61.2)	To maintain in a normal ET_{PCO_2} , RR and SpO_2 ranges
Initial settings	IBW, humidification system, medical history	IBW, medical history
Setting modification displayed but need caregiver prescription (open loop)	No	Yes
Input data	$_{2min}V_t$, $_{2min}RR$, $_{2min}ET_{PCO_2}$, PEEP, PS level, ventilator messages	RR, ET_{PCO_2} , SpO_2
Rules displayed to caregivers when applied	No	±
Output data	Parameter display, e.g. PS level Therapeutic messages “SBT successful”	MV, PEEP, FiO_2 SBT duration
SBT	Yes	Yes
SBT duration	1–2 h according to initial PS level (Jouvet et al. 2007)	Adjustable
Recommendation of separation from the ventilator	Yes	No

PS pressure support, ASV adaptive support ventilation, IBW ideal body weight for height, V_t tidal volume, RR respiratory rate, ET_{PCO_2} end-tidal PCO_2 , SpO_2 pulse oxygen saturation, $_{2min}V_t$, $_{2min}RR$ or $_{2min}ET_{PCO_2}$ mean value on 2 min of V_t , RR or ET_{PCO_2} , MV minute volume, PEEP positive end-expiratory pressure, FiO_2 inspired fraction of oxygen, PIP positive inspiratory pressure, SBT spontaneous breathing trial

Jouvet et al. 2010a). These weaning criteria are as follows:

- The attending physician evaluates that the patient is able to breathe spontaneously or the patient is already breathing spontaneously.
- No significant vasopressors or inotropic medications, excluding digoxin or low-dose dopamine ($\leq 5 \mu\text{g/kg/min}$).
- Slight or no endotracheal tube gas leakage ($[V_{ti}-V_{te}]/V_{ti} \leq 20\%$).
- Mechanical ventilation with a plateau pressure above PEEP $\leq 25 \text{ cmH}_2\text{O}$.
- PEEP $\leq 8 \text{ cmH}_2\text{O}$.
- $FiO_2 \leq 60\%$ with $SpO_2 \geq 95\%$.
- Pressure support test passed. During the pressure support test, the patient is mechanically ventilated in pressure support mode for 30 min, with a level of pressure support set to $\pm 5 \text{ cmH}_2\text{O}$ of the current plateau pressure. The pressure support test is stopped before 30 min

if the patient shows evidence of respiratory distress (respiratory rate below 10 breaths per min or above 40 breaths per minute and $FiO_2 > 60\%$ in order to obtain a $SpO_2 \geq 95\%$). The test is passed when, after 30 min, the patient remains stable with a respiratory rate between 10 and 40 breaths per min, an expiratory tidal volume higher than 6 ml/kg and $SpO_2 \geq 95\%$ with $FiO_2 \leq 0.6$.

When the child fulfils all the above mentioned criteria, IBW, which is also a surrogate for lung volume (see chapter on explicit computerised protocols), is prescribed on the ventilator by the user. The next step is to prescribe the humidification system and the medical history (presence or not of neurologic disorders or COPD) if the child's IBW is above 35 kg. These user-given settings will determine certain thresholds and specific rules of the ECP (Table 61.2).

Table 61.2 Normal ventilation definition in SmartCare/PS®

Definition	Parameters value	IBW ≤35 kg	35 kg <IBW ≤55 kg	IBW >55 kg
Normal ventilation:	RR low (bpm)	18	10–15	10–15
RR low ≤ RR < RR high	RR high (bpm)	40	20–40 34 for COPD & neurological disorders	20–40 34 for COPD & neurological disorders
V_T low ≤ V_T	V_T low	6 ml/kg	250 ml	300 ml
$ET_{PCO_2} < ET_{PCO_2}$ high	ET_{PCO_2} (mmHg)	55	45–65 65 for COPD	45–65 65 for COPD
RR max (bpm)		50	36	36

IBW ideal body weight, COPD chronic obstructive pulmonary disease

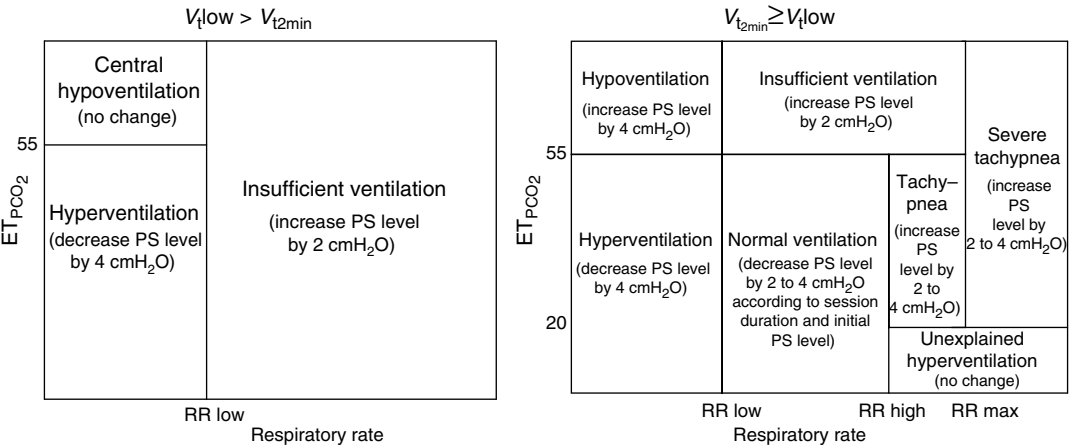


Fig. 61.2 Classification of ventilation by SmartCare/PS® Draeger Medical. Pressure support level is modified according to values of tidal values (below V_{Tlow} : panel a, above V_{Tlow} : panel b), respiratory rate and end-tidal PCO_2

at 2–5 min intervals (SmartCare waits 2 min for the next “Classification of Ventilation” if PS was not changed and waits 5 min if PS was changed (either by SmartCare or by the user))

61.2.1.2 Primary Goal: To Safely Maintain the Child in a Zone of Respiratory Comfort (Normal Ventilation)

In contrast to conventional ventilation modes, SmartCare/PS® continuously adapts the pressure support level to maintain normal ventilation. Normal ventilation corresponds to a respiratory pattern that is determined by lower and upper thresholds of tidal volume, respiratory rate and ET_{PCO_2} (Table 61.2). In turn, these thresholds are defined within acceptable limits as reported by a large panel of paediatric intensivists (Santschi et al. 2007). To keep the patient in normal ventilation, the pressure support level is increased or decreased according to the implemented rules of the knowledge base that represents the ECP (Fig. 61.2) (Mersmann 2009).

61.2.1.3 Weaning of Ventilatory Support

When the child remains in normal ventilation for a predefined period of time (60, 30 and finally 15 min), the PS level is gradually decreased (Jouvet et al. 2007), which is called a regular weaning step. During the entire execution of the ECP, duration of stability and duration of instabilities are balanced and taken into account when assessing the patient’s needs. When the patient’s respiratory pattern is outside the limits of normal ventilation, an instability is noted. A maximum of two instabilities will be tolerated by SmartCare/PS® before the pressure level will be increased.

61.2.1.4 Spontaneous Breathing Trial

An automated SBT is started if the patient is in normal ventilation at a predefined minimal

Table 61.3 Spontaneous breathing trial on SmartCare/PS® and IntelliVent®

	SmartCare/PS®	IntelliVent®
<i>Criteria to start SBT:</i>		
PIP (cmH ₂ O)	≤5 ^a , ≤7 ^b , ≤9 ^c or ≤10 ^d	0–50 (adjustable)
PEEP (cmH ₂ O)	≤5–15 (adjustable)	0–25 (adjustable)
FiO ₂	≤0.3–1 (adjustable)	0.21–1 (adjustable)
Spontaneous ventilation	Patient with normal ventilation (Table 61.2)	Spontaneous breath percentage (adjustable between 0 and 100 %)
Others		RSB, variability index or $P_{0.1}$
SBT duration	1 h if initial PS level ≤22 cmH ₂ O	Adjustable
	2 h if initial PS level >22 cmH ₂ O	

SBT spontaneous breathing trial, PS pressure support, RSB rapid shallow breathing

^aPatient >35 kg, tracheotomised with active or no humidification

^bPatient >35 kg, endotracheally intubated with active or no humidification

^cPatient >35 kg, tracheotomised, with heated/moisture exchange filter

^dPatient ≤35 kg or >35 kg, endotracheally intubated, with heated/moisture exchange filter

pressure support level, PEEP level and FiO₂ below preset thresholds (Table 61.3). When the SBT is successfully passed, a message is displayed on the ventilator. Caregivers have to decide whether the patient may be extubated. If the patient is not extubated, SmartCare/PS® continues to be active trying to preserve the therapeutic success, and if the patient's spontaneous breathing may become unstable afterwards, SmartCare/PS® maintains or cancels the SBT successful message depending on the level of the instabilities.

61.2.2 SmartCare/PS® in Clinical Practice

Among the first 20 paediatric patients treated with SmartCare/PS®, median time in normal ventilation was 91 % (range, 0.7–99 %) (Jouvet et al. 2007).

The median number of changes in the pressure support level over the entire study period was 1.5 changes per hour (range, 0.7–8.2). Variation of pressure support level was mostly due to low tidal volume and high respiratory rate (> 95 %), although a few changes were due to low respiratory rate or high ET_{PCO₂}.

We reported two clinical trials on SmartCare/PS® in children (Jouvet et al. 2007; Jouvet et al. 2010a). In the randomised clinical trial (RCT) at Sainte Justine Hospital–Montreal (Canada), a significant decrease in weaning duration in the SmartCare/PS® group ($n=15$) was observed when compared to usual care ($n=15$), without any modification in weaning failure rates (Jouvet et al. 2010a). These results need to be validated in a multicentre RCT especially because the positive impacts of SmartCare/PS® can vary from one PICU to another. This was observed in adult ICUs showing a real improvement in an European RCT (Lellouche et al. 2006) as well as no significant impact in a pilot RCT in Australia (Rose et al. 2008). The various impact of SmartCare/PS® across ICUs can be due, at least partially, to different organisation of mechanical ventilation. For example, in the pilot RCT in the adult Australian ICU, weaning in the study ICU was performed by experienced and relatively autonomous nurses, using a 1:1 nurse-to-patient ratio maintained over all shifts. This was not the case in the European centres.

The major strength of SmartCare/PS® is the implementation of an automated evidence-based ECP for mechanical ventilation with a user-friendly interface that allows individual customisation. According to Chatburn and Deem (2007), evidence-based ECPs provide many benefits like increased adherence to evidence-based interventions, reduced practice variability, improved outcomes, improved safety and enhanced education. There are several improvements to consider surrounding SmartCare/PS®: (1) step 1 of weaning is not included so far (Fig. 61.1). The need to switch to pressure support mode prior to consider SmartCare/PS® requires that caregivers have first to evaluate if the patient can breathe spontaneously. (2) Children with IBW below 15 kg are excluded. Therefore, another

ECP is needed in the same PICU for infants. (3) PEEP and FiO_2 are not automatically adjusted by SmartCare/PS® but are recommended criteria to SBT initiation.

61.3 IntelliVent®: Hamilton Medical

IntelliVent® is an explicit computerised protocol for the automated control of minute volume, PEEP and FiO_2 in adaptive support ventilation (ASV). IntelliVent® manages, with (open loop) or without the need of caregiver's intervention (closed loop), the four following weaning steps: (1) switch from control ventilation to spontaneous breathing (specificity of ASV mode; see chapter on ASV); (2) automatic adaptation of the pressure to maintain the patient in a range of respiratory rate, ET_{PCO_2} and SpO_2 ; (3) an automated SBT when children reach a minimum ventilatory support; and 4) a timer that shows SBT duration (Table 61.1). IntelliVent® is only available on new generation of Hamilton Medical ventilators (Hamilton S1) that continuously monitor usual mechanical ventilation parameters plus ET_{PCO_2} and SpO_2 .

61.3.1 Description of IntelliVent®

IntelliVent® has two automated adjustment features: one is the automatic minute volume adjustment (CO_2 controller), the other one is the automatic FiO_2 and/or PEEP adjustment (O_2 controller). These two controllers can be set to manual or automatic. In manual mode, the controllers displayed a recommendation for the adjustment of minute ventilation, FiO_2 or PEEP (open loop). In automatic mode, the adjustments of minute ventilation, FiO_2 and/or PEEP are instantaneously corrected (closed loop). The CO_2 and O_2 controllers can be activated separately.

61.3.1.1 IntelliVent® (CO_2 and O_2 controllers) Start Criteria

IntelliVent® can be activated as soon as the patient is ventilated in ASV mode. This explicit

computerised protocol is designed to manage the ventilator course of children with various diseases (ARDS, COPD, brain injury). In the lack of evidence of ventilatory support using IntelliVent® in the acute phase in paediatrics, we will focus this section on the management of the weaning phase.

IntelliVent® can be prescribed when a child, with $\text{IBW} \geq 7$ kg, fulfils readiness to wean criteria that were used in a prospective clinical trial (NCT01095406) (Jouvet et al. 2010b). These weaning criteria are the same criteria used for Smartcare/PS®. In addition, it is recommended to validate that ET_{PCO_2} is correlated to blood gas PCO_2 (gap between ET_{PCO_2} and $\text{PCO}_2 \leq 7$ mmHg on last blood gas). Pressure support test is not an obligation as assisted breath (pressure support) is given to the patient as soon as the patient is able to trigger the breath (see section 8.1.3.3.3 on Adaptive Support Ventilation).

61.3.1.2 CO_2 Controller

Primary goal of CO_2 controller: to adjust minute volume to patient needs.

ASV uses a pressure-controlled, synchronised time-cycled breathing pattern and maintains operator preset minimum minute for ventilation independent of the patient's spontaneous breathing activity. Minute volume is based on IBW calculated from the body height. The target breathing pattern (tidal volume and respiratory rate) is calculated using Otis' equation (Otis et al. 1950), based on the assumption that the optimal breathing pattern results in the least work of breathing. In addition, a lung protection strategy ensures permissive hypercapnia in the acute phase.

The CO_2 controller aims to increase or decrease minute volume with a maximum change of 1 % minute volume per breath. The modification of minute volume is different when the patient is breathing spontaneously (patient active) or not (patient passive). The patient is considered passive if there are more than three consecutive mechanical breaths without any patient effort. The patient is considered active when three to five consecutive mechanical breaths are triggered by the patient's own inspiratory effort.

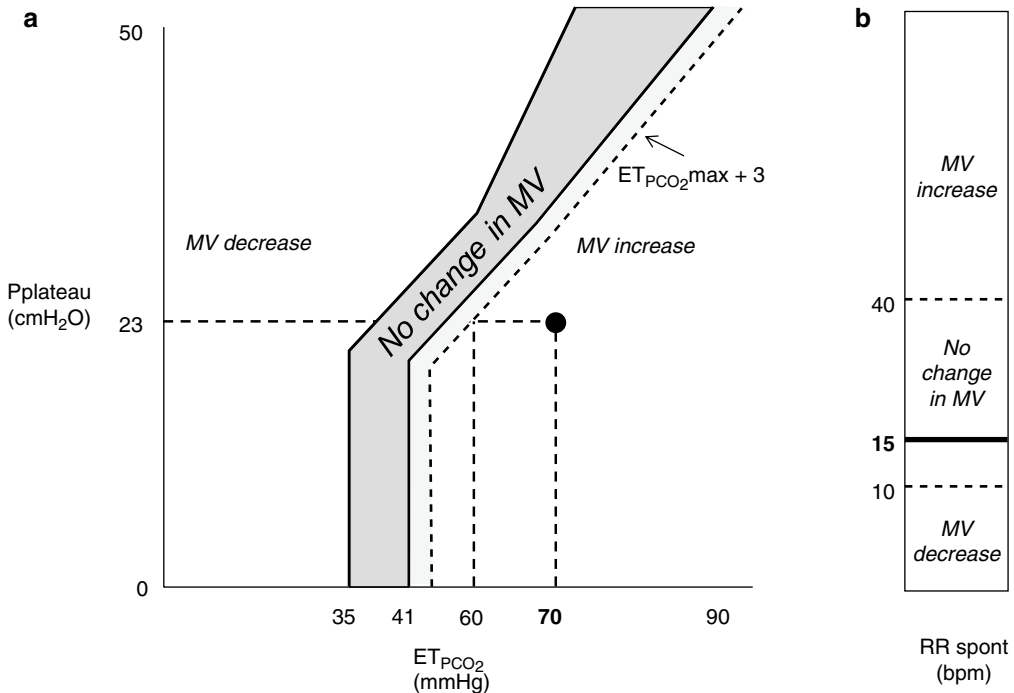


Fig. 61.3 CO₂ controller algorithm to modify minute volume (MV) according to end-tidal PCO₂ (ET_{PCO₂}) in patients without any respiratory efforts (panel a) and in patients with respiratory efforts (panel b). In addition, if spontaneous respiratory rate is within the optimal range but ET_{PCO₂} > ET_{PCO₂} maximum + 3 mmHg (see threshold in panel a), MV will also be increased. Two examples: (1) a patient without any spontaneous breath, with a plateau pressure of 23 cmH₂O and ET_{PCO₂} of 70 mmHg will have an

increase of minute volume by 1 % of MV per breath until the ET_{PCO₂} will be in the grey area ("no change of MV") unless the increase of plateau pressure or minute volume reach upper ventilator alarm limits. (2) A patient breaths spontaneously at 15 spontaneous breaths per minute and plateau pressure is 23 cmH₂O; he will have an increase of minute volume by 1 % of MV per breath if ET_{PCO₂} is above 60 mmHg (see panel a). MV will increase until the ET_{PCO₂} will be in the grey area of panel a ("no change of MV")

- Patient passive: When there is no spontaneous breath, the CO₂ controller increase or decrease minute volume in order to maintain ET_{PCO₂} in an optimal range. A permissive hypercapnia ventilation is implemented resulting in increase and larger optimal ET_{PCO₂} range when plateau pressure increases (Fig. 61.3 panel a).
- Patient active: When the patient is breathing spontaneously, minute volume is mainly adjusted to maintain respiratory rate within optimal range according to spontaneous respiratory rate (see Fig. 61.3 panel b). In addition, if spontaneous respiratory rate is within the optimal range but ET_{PCO₂} > ET_{PCO₂} maximum + 3 mmHg (Fig. 61.3 panel a), then the CO₂ controller increases minute volume until ET_{PCO₂} ≤ ET_{PCO₂} maximum.

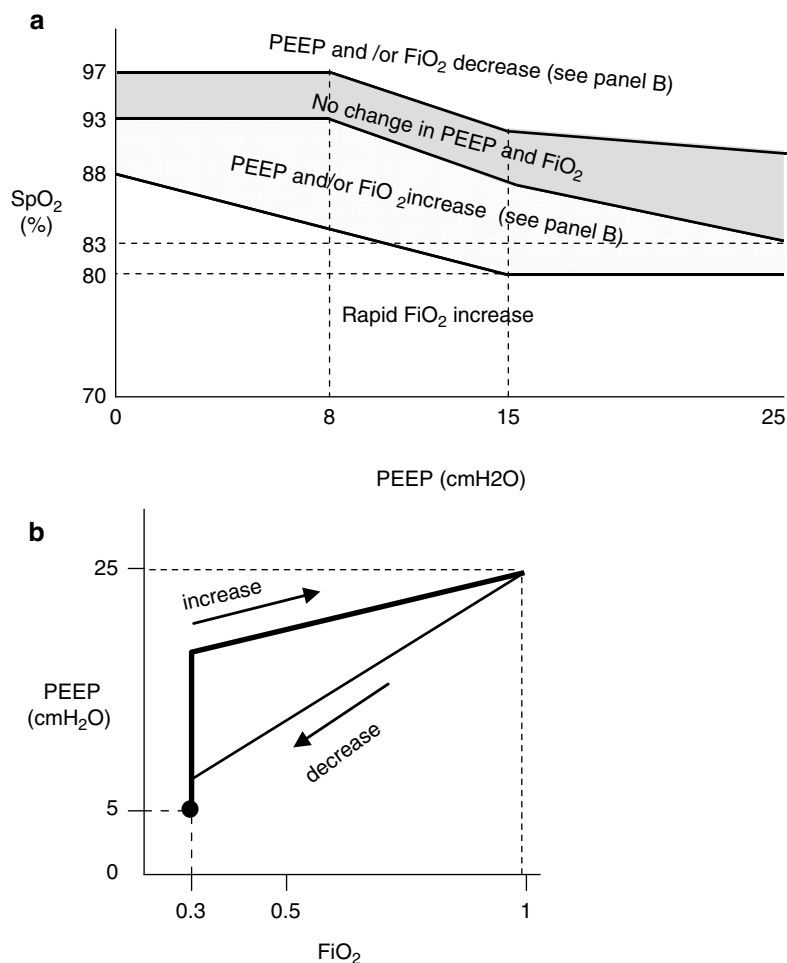
61.3.1.2.1 Decrease of Ventilatory Support

The CO₂ controller adapts minute volume to patient's needs and positive pressure is decreased according to improvements in lung mechanics.

61.3.1.2.2 Spontaneous Breathing Trial

Caregivers can set several criteria for SBT start, including FiO₂, PEEP, MV, PIP above PEEP, spontaneous breath percentage (average of the percentage of spontaneous breaths over the last 8 total breaths) and eventually one of the three following weaning indexes: rapid shallow breathing, variability index or P_{0.1}. When these criteria are all fulfilled, an SBT timer starts. Caregivers also have to define the SBT duration before considering separation from the

Fig. 61.4 O₂ controller algorithm to modify PEEP and FiO₂ according to actual SpO₂. Panel **a**: thresholds of SpO₂ to increase or decrease PEEP and/or FiO₂. A specific algorithm increases rapidly FiO₂ when SpO₂ is below a minimum threshold. Panel **b**: the algorithm used to modify PEEP and FiO₂ is shown. The algorithm on PEEP/FiO₂ adjustments is a mixture of the ARDS network protocol (The Acute Respiratory Distress Syndrome Network 2000) and the higher PEEP algorithm after protocol changed scales (Brower et al. 2004). Caregivers can activate only FiO₂ or only PEEP or both PEEP and FiO₂ adjustments



ventilator. Further research is needed to validate SBT criteria.

61.3.1.3 O₂ Controller

Primary goal of O₂ controller: to adjust PEEP and/or FiO₂ to actual SpO₂. PEEP and FiO₂ can be automatically adjusted according to the SpO₂. The O₂ controller consists of two separate adjustments:

- A rapid response FiO₂ adjustment that controls FiO₂ on a breath-by-breath interval. The rapid response FiO₂ sets FiO₂ to 1 as soon as SpO₂ is below the lowest acceptable value (Fig. 61.4 panel a).
- A regular PEEP and/or FiO₂ adjustment which controls PEEP and FiO₂ using a longer control interval. In the regular PEEP/FiO₂ adjustment, the algorithms used to modify PEEP and FiO₂

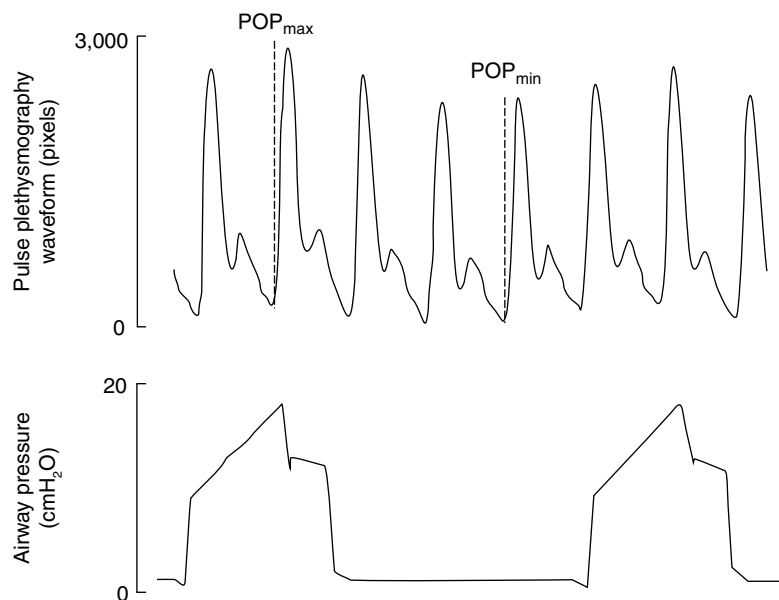
are shown in Fig. 61.4. Caregivers can choose only FiO₂, only PEEP or both PEEP/FiO₂ automatic adjustments. In addition to PEEP increase, automatic recruitment manoeuvre, applying pressure of 40 cmH₂O for 20 s, can also be activated.

61.3.1.3.1 PEEP Thresholds

PEEP can automatically decrease to 5 cmH₂O according to patient conditions. PEEP can also increase until an upper threshold is reached. This threshold can be set by users. In the absence of clinical experience, if automatic PEEP is activated, we recommend an upper PEEP threshold of 8 cmH₂O, in children.

The caregiver can also set the patient condition as “haemodynamic unstable” at O₂ controller

Fig. 61.5 Heart-Lung Index (HLI). HLI assesses the interaction between airway pressure and haemodynamics parameters as analysed by the pulse oximeter plethysmogram (POP). HLI is calculated as

$$\text{HLI (\%)} = \frac{(\text{POP}_{\text{max}} - \text{POP}_{\text{min}})}{(\text{POP}_{\text{max}} + \text{POP}_{\text{min}})} * 100/2$$


start. PEEP is then limited to 8 cmH₂O and no recruitment manoeuvre is performed.

During O₂ controller function, a heart lung interaction index (HLI) is also continuously monitored from the pulse oximeter (Fig. 61.5). The HLI reflects how much airway pressure interacts with haemodynamics. If HLI >15 %, it means high interaction. In such a case PEEP increase is limited, FiO₂ increase is preferred and no recruitment manoeuvre is performed. If no HLI value is available, a user message is given and PEEP is limited to 8 cmH₂O.

61.3.2 IntelliVent® in Clinical Practice

In adults, two clinical trials were conducted. Arnal et al. (2010) conducted a prospective randomised crossover controlled trial comparing ASV and IntelliVent® in 43 adult patients with acute respiratory failure. In this trial, the patients ventilated with IntelliVent® spent more time with optimal ventilation and had lower volumes and pressures for equivalent results on gas exchange. Lellouche et al. (2010) conducted a prospective randomised controlled study comparing usual care versus IntelliVent® in post cardiac surgery adult patients. The patients ventilated with IntelliVent® spent also more time with optimal ventilation.

IntelliVent® has been assessed in one research trial on feasibility and safety in children. The preliminary report (Jouvet 2010) for the first 12 children included during the weaning phase concluded that (1) the CO₂ controller was adapted for children. ET_{PCO₂} monitoring was accurate. The specific medical diagnosis (ARDS, COPD, “push to wean”) were helpful for ET_{PCO₂} thresholds adjustments which in addition can be further adjusted by ±5 mmHg. The development of an additional algorithm that tests the ability of children to breathe alone can improve CO₂ controller efficacy to wean all patients. (2) The O₂ controller manages FiO₂ adequately according to SpO₂ monitoring. PEEP-FiO₂ algorithm resulted in frequent modifications of PEEP that did not correspond to current clinical practice in paediatrics at Sainte Justine Hospital–Montreal (Canada). Therefore, PEEP management needs further study in children. (3) In the absence of Heart-Lung Index (HLI) assessment, the preset upper PEEP level at 8 cmH₂O at IntelliVent® start in children is recommended. (4) The use of IntelliVent® is not recommended in children with tracheal tube air-leak >20 % (use of a cuffed tube is recommended) to ensure that minute volume prescribed is closed to minute volume delivered.

The major strength of IntelliVent® is the implementation of an automated ECP for mechanical

ventilation with a user-friendly interface that allows individual customisation of the whole ventilation course including CO₂ removal and O₂ delivery. Many components of this ECP are adjustable, and recruitment manoeuvres can be automated according to clinical practice in PICU. There are several improvements to consider surrounding IntelliVent®: (1) At present, there is not much clinical experience with this ECP. (2) Children with IBW below 7 kg are excluded. Therefore, another ECP is needed in the same PICU for younger children. (3) Automatic PEEP adjustment needs further research (see above). (4) Heart-Lung Index needs also further research to validate its use to limit PEEP increase.

Conclusions

The two explicit computerised protocols for weaning from mechanical ventilation are implemented by companies in one specific mode of ventilation (PSV or ASV). They either manage CO₂ removal settings (SmartCare/PS®) or both CO₂ removal and O₂ delivery settings (IntelliVent®). The main innovation of the two ECPs is the use of ET_{PCO₂} as a surrogate for blood gas PCO₂, to decrease or increase ventilatory support. This seems appropriate when the patient's own inspiratory effort trigger ventilatory support because the ECP assumes that the central respiratory command is able to set minute volume and ET_{PCO₂} is used to detect any failure in the respiratory command or muscle strength. When the patient is passive (no inspiratory effort), IntelliVent® is the only ECP available so far that is able to manage CO₂ removal. ET_{PCO₂} becomes a crucial input data for CO₂ removal. Paediatric caregivers are not routinely used to manage mechanical ventilation according to ET_{PCO₂} levels, and further research is mandatory to validate this point.

One of these ECP opened also a new area in the management of O₂ delivery. IntelliVent® adapts FiO₂ and PEEP according to SpO₂. In clinical practice, SpO₂ is nowadays a key input data to manage FiO₂ and specific recommendations for the simultaneous management of PEEP and FiO₂ have been published by the

ARDS network and other research teams (The Acute Respiratory Distress Syndrome Network 2000; Brower et al. 2004). Then, an ECP that manages both PEEP and FiO₂ according to SpO₂ is logical. In clinical practice, several other factors also influence the prescription of PEEP including haemodynamic state and regional distribution of ventilation (on chest X-ray or tomodensitometry). To take into account these factors, IntelliVent® has specific surrogates for these factors, including patient condition prescription (e.g. "ARDS patient", "brain injury", "haemodynamic unstable") and HLI (surrogate of haemodynamic instability). Further research in children is needed to validate their use.

The large amount of information collected in this book demonstrates that we now need to synthesise our knowledge. Explicit computerised protocols are one way to synthesise and standardise care in mechanical ventilation with individual customisation. The two ECP described here are the innovators. Further research is needed to better assess the efficacy and tolerance of these two ECPs in children and to develop ECP that are dedicated to all ages including neonates.

Essential Point

SmartCare/PS® and IntelliVent® are new explicit computerised protocols that need further research in children.

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62.1 Role of Computerized Decision Support Tools in Studies Involving Lung Protection Strategies of Mechanical Ventilation

Educational Goals

- To understand that although the basic principles of lung protective ventilation have been embraced by pediatric intensive care physicians, it is unlikely that replicable and consistent decisions are made to minimize ventilator support across the duration of mechanical ventilation for patients with acute lung injury and acute respiratory distress syndrome.
- To understand the use of decision support tools is a response to variation in

clinical medical practice due in part to clinicians' poor compliance with guidelines and recommended therapies.

- To consider that decision support tools (paper or electronic) have been shown to improve the quality of medical care, reduce errors, and improve patient outcomes. However, paper-based tools can be difficult to follow accurately, leading to low adherence rates.

While the basic principles of lung protective ventilation have been embraced by pediatric intensive care physicians, there is still great variability in ventilator management (Santschi et al. 2010). Although most critical care practitioners believe they are being lung protective, it is likely that replicable and consistent decisions are not made to minimize ventilator support across the duration of mechanical ventilation for patients with lung injury.

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The use of decision support tools is a response to variation in clinical practice due in part to clinicians' poor compliance with guidelines and recommended therapies. Computerized protocols used to deliver decision support can be configured to contain much more detail than textual guidelines or paper-based flow diagrams. Such protocols can generate patient-specific instructions for therapy that can be carried out with little interclinician variability (Morris 2000). Computer decision support tools (computer protocols) have been shown to improve the quality of medical care and have been cited by the Institute of Medicine (Kohn et al. 1999) as a method to reduce medical errors. Such tools aim to ensure replicable, evidence-based clinician decisions for equivalent patient states and to improve protocol compliance. Much of the research on computer protocols in the intensive care unit (ICU) has been focused on adult ICUs (Morris 2000; East et al. 1999). Little is known about the use of adult-derived computer decision support tools in pediatric medicine. The first application (Mullett et al. 2001) of an anti-infective tool appeared to be beneficial to children and allowed cost savings. The second, a glucose/insulin protocol (Morris et al. 2008), also appears to be as applicable to children as it is to adults (Thompson et al. 2008). This study also confirmed high compliance (>97 %) compared with a paper protocol and tighter adherence to the target range. While children are developmentally and physiologically not "little adults" (Newth 1979, 1986), it appears that at least some computer decision support protocols could be used in both adults and children. Adult protocols seem likely to need modification in the granularity (detail) of the decision rules to be usable in children and research needs to be done to investigate this issue (Fig. 62.1).

While a computer-based protocol has been developed for adult ARDS, large differences between adult and pediatric critical care bring into question the practice of extrapolating adult evidence regarding ventilator management with computer protocols to children with ALI/ARDS. In particular, pediatric practice may tolerate only smaller (more granular) changes of 0.05 in the fraction of inspired oxygen, rather than the 0.1

increments in the adult ARDSNet protocol, as suggested by our analysis of large datasets from both Vanderbilt Children's Hospital and Children's Hospital Los Angeles (Khemani et al. 2009a). Also, the ranges of pH used in the ARDSNet protocol for changes in ventilator rate and tidal volume may be too broad for many pediatric intensivists. There are also differences in how predicted body weight from height/length is calculated for determination of tidal volumes in lung protective volume-controlled modes, with pediatricians needing to deal with failure to thrive, contractures, and obesity, with only the latter being of real importance to adult practitioners. It is probable that measurement of ulna length will prove to be the best and safest predictor of height and the subsequent percentile for age used to calculate weight and thence tidal volume over the entire pediatric age range (Gauld et al. 2003; von Ungern-Sternberg et al. 2009). The adult protocol calls for recording the set volume delivered by the ventilator, whereas pediatric practice is to measure the tidal volumes directly, but has not been standardized to either in the ventilator or at the endotracheal tube (ETT), with large differences recorded between the two (Al-Majed et al. 2004; Rosen et al. 1993; Stenson et al. 1998). Finally, adult protocol management of ALI is based on A/C volume control, a mode rarely used by pediatric intensivists who seem to prefer pressure-regulated modes.

Decision support tools (paper or electronic) have been shown to improve the quality of medical care (Shortliffe and Cimeno 2006), reduce errors (Slonim and Pollack 2005), and improve patient outcomes (Blaser et al. 2007). However, paper-based tools can be difficult to follow accurately, leading to low adherence rates—30 % compliance in a pediatric ventilator study with a paper protocol (Randolph et al. 2002) compared with 94 % in an adult ventilator management study with a computer-based protocol (Morris et al. 1994). Computers can assist clinicians by standardizing descriptors and procedures, by consistently performing calculations, by incorporating complex rules with patient data, and by capturing data relevant to decision making (Clemmer 2004; Morris 2003; Morris et al. 1996). Computer-based protocols can contain

eVentilator - Default Rule Set

File Tools Help

Patient Information

Unit Number: [] Physician: [] Height (cm): 59 (3%) Ulna Length: [] ?

Patient Name: [] Resident: [] Weight (kg): 6.45 (40%) Pred. Wt. (kg): 4.8

Date of Birth: [] ICU Admit: [] HC (cm): 38.5 LOS (days): 6.8

Gender: [] Service: [] Age: 4 Mos ICU Bed: 2E-L

Ventilator Mode Info

☐ Volume Control ☐ PRVC

☐ High Frequency Oscillation ☒ Pressure Control

Parameters Blood Gas Baseline CXR Import Data

Ventilator Rate: [] pH: [] E

VT (ml/kg): [] pCO2: []

PIP: [] FiO2: []

PEEP: [] PaO2: []

MAP: [] SpO2: []

S/F Ratio: N/A OSI: N/A LIS: N/A **Nomogram**

P/F Ratio: N/A OI: N/A VI: N/A **Evaluate**

Warnings:

120 Minutes Until Next Evaluation

Simulate Oxygenation Table Ventilation Table Select Patient Exit

Current Recommendation:

Recommendation History:

Fig. 62.1 The presenting screen of a computer decision support tool prepared for pediatric modes of ventilation. Specific tools are within the software including the oxygenation tables for various levels of PaO₂ or SpO₂ and PEEP, ventilation tables for various levels of pH, VT and PIP,

chest film assessment for the lung injury score, nomograms for acid-base balance, predicted body weights from 0 to 19 1/2 years of age, and the application of ulna length for prediction of height and thus ideal weight in children who are either obese or have failed to thrive or have contractures

extensive detail, while at the same time protecting the user from complexity and information overload. These tools aim to ensure flexible but consistent, evidence-based clinician decisions for equivalent patient states. Management of mechanical ventilation is an iterative treatment protocol encompassing many individual decisions that must be made over the course of a patient's treatment, usually by multiple practitioners. Replicable ventilator management decisions would help decrease practice variability and would likely directly shorten the length of mechanical ventilation for children in pediatric ICUs (Jouvet et al. 2007). While the ARDS network has developed computer-based mechanical ventilation protocols for adults with ALI and ARDS, it is unlikely that a computer protocol for ventilator management developed in the adult ICU can simply be deployed in the pediatric set-

ting. The protocol must be translated to ensure that it accurately reflects unique aspects of pediatric practice; and it must be evaluated in a rigorous, formal manner to ensure that it is safe, effective, and appropriately sized.

A computer-based pediatric mechanical ventilation protocol, adapted from published ARDS Network Oxygenation and Ventilation tables (ARDSNet 2000), has been created for use in pediatric trials of ALI and ARDS. The ventilation modes have been expanded from volume control to include PC, PRVC, and high-frequency oscillatory ventilation (HFOV—theoretically the most lung protective of all modes, which has never been properly tested in pediatric ALI/ARDS with an adequately powered study) (Fig. 62.2).

The tables have been refined iteratively, to reflect the consensus of a number of pediatric critical care physicians and investigators from the

eVentilator - Default Rule Set

File Tools Help

Patient Information

Unit Number: [Redacted] Physician: [Redacted] Height (cm): 59 (3%) Ulna Length: [Redacted] ?
 Patient Name: [Redacted] Resident: [Redacted] Weight (kg): 6.45 (40%) Pred. Wt. (kg): 4.8
 Date of Birth: [Redacted] ICU Admit: [Redacted] HC (cm): 38.5 LOS (days): 6.8
 Gender: [Redacted] Service: [Redacted] Age: 4 Mos ICU Bed: 2E-L

Ventilator Mode

☐ Volume Control ☐ PRVC
☐ High Frequency Oscillation ☒ Pressure Control

Parameters Blood Gas Baseline CXR Import Data

Ventilator Rate: 24 pH: 7.29 E
 VT (ml/kg): [Redacted] pCO₂: [Redacted]
 PIP: 34 FiO₂: 1.0
 PEEP: 10 PaO₂: 85
 MAP: 16 SpO₂: 93

S/F Ratio: 93 OSI: 17 LIS: 3.5 Nomogram
 P/F Ratio: 85 OI: 19 VI: N/A Evaluate

Warnings:

Patient currently meets P/F definition for ARDS.

120 Minutes Until Next Evaluation

Accept/Decline Recommendation

Ventilation Recommendation

Leave PIP=34 ; Set VR=29 (Recommendation modified to maintain delta P) ☐ Accept ☐ Decline

If declined, why? [Redacted]

Oxygenation Recommendation

Set FiO₂=0.95 ; Keep PEEP at 10 (Decrease FiO₂ 0.05) ☐ Accept ☐ Decline

If declined, why? [Redacted]

Extubation Readiness Test (Optional)

Is pt breathing spontaneously? ☐ Yes ☐ No
 Test for extubation readiness? ☐ Yes ☐ No Show Guideline

OK

Fig. 62.2 Examples of recommendations and calculations provided to the bedside clinicians by the computer decision support for an infant with ARDS from adenovirus pneumonia, on Pressure Control mode ventilation

National Institutes of Health funded Collaborative Pediatric Critical Care Research Network and the Pediatric Acute Lung Injury and Sepsis Network. However, such protocols need to be tested to divine whether they describe current pediatric lung protective practices and evaluate whether the adapted protocol is in line with this practice. This can be done by comparing ventilator protocol recommendations to actual changes in mechanical ventilation derived from databanks of ventilation, oxygenation, and blood gas data collected over recent years while applying such lung protective strategies. Areas with high variability or in which clinical practices are not in line with the protocol will likely have the largest potential impact to change and standardize clinical practice (Khemani et al. 2010). Such areas include the time between inspired oxygen decreases appropriate for improving oxygenation, time, and magnitude of PEEP increases to limit excessive

inspired oxygen increases and investigating whether it is better to target a specific tidal volume (e.g., PRVC mode) with the inherent risks of over- or underinflation as opposed to limiting pressures (e.g., PC mode) where tidal volume is allowed to vary with the degree of lung injury (Khemani et al. 2009b).

In a retrospective study (Khemani et al. 2010) of the years 2000–2207 from a single institution (Children's Hospital Los Angeles), data were extracted for 402 children on pressure-control ventilation with PaO₂/FiO₂ (P/F) ratio <300. Approximately 2,700 arterial blood gas values and 6,000 ventilator settings were analyzed against this pediatric computer protocol for PC mode. Changes to PEEP, FiO₂, PIP, and ventilator rate recommended by the protocol were compared to actual changes. The median P/F ratio was 140, with 24.4 % mortality. The computer protocol recommended decreasing FiO₂ for

54.3 % of clinician decisions; however, FiO_2 was actually decreased in only 29.3 % of these decisions. In the mid (55–68 mmHg) and low (<55 mmHg) PaO_2 ranges, the computer protocol recommended more PEEP than was used in actual practice, 42 and 67 % of the time, respectively. Changes to PIP or VR after an ABG were consistent with the protocol 42 % of the time, but the most common clinical decision was no change to either PIP or VR (46 %). This was true even when pH was >7.45 and PIP was ≥ 30 cmH_2O . Changes in ventilation were made on average every 4 h. It is not unrealistic to believe that decision support protocols utilizing noninvasive markers of oxygenation and ventilation and which provide reminders to caregivers at set time intervals can speed up this process and decrease the time of exposure to high pressures, volumes, and inspired oxygen concentrations.

The clear thought processes required for the development of computer-based decision support tools for the different modes of mechanical ventilation is the first step in automating ventilator management in studies of specific entities such as ARDS. For the moment, at least in the USA, this will remain an open-loop system, where a physician must look at each recommendation and approve or disapprove its implementation. In the future, it will inevitably become a closed-loop system, particularly aided by the refinement of noninvasive markers of oxygenation (Khemani et al. 2009a) and ventilation, such as the already-available commercial system (outside the USA) for regulation of inspired oxygen to maintain an acceptable pulse oximetry value in neonatal practice (Claure et al. 2009). Jouvét et al. (2007) in Canada are already implementing a closed-loop system for ventilation utilizing respiratory rate and minute ventilation as well.

Essentials to Remember

- Replicable ventilator management decisions should help decrease practice variability and will likely directly shorten the length of mechanical ventilation for children in pediatric ICUs.

- A computer-based pediatric mechanical ventilation protocol, adapted from published ARDS Network Oxygenation and Ventilation tables, has been created and is intended for use in pediatric trials of ALI and ARDS.
- The *adult* protocol tables have been refined iteratively to reflect the consensus of a number of *pediatric* critical care physicians and investigators. However, such a protocol needs to be tested by numerous practitioners to evaluate whether the adapted protocol is in line with current pediatric practice.

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Part XXIV

Long-Term Outcomes After Mechanical Ventilation

Long-Term Outcomes After Mechanical Ventilation in Neonates

63

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Abbreviations

BPD	Bronchopulmonary dysplasia
COPD	Chronic obstructive pulmonary disease
IPPV	Intermittent positive pressure ventilation
RDS	Respiratory distress syndrome
RSV	Respiratory syncytial virus
VLBW	Very low birth weight

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Educational Goals

To review the literature on long-term outcomes following neonatal mechanical ventilation particularly on:

- Respiratory function
- Exercise capacity
- Other aspects of respiratory health
- Neurodevelopment

63.1 Introduction

The introduction of assisted ventilation over the past 40 years has been important in improving survival rates of infants suffering from respiratory compromise (Ambalavanan and Carlo 2006; Doyle et al. 1996). Neonates are vulnerable to respiratory failure due to a number of features in their developmental physiology. For instance, they have a high metabolic rate, decreased lung compliance, decreased functional residual capacity and increased airways resistance, and, when preterm or septic, some have reduced levels of surfactant, including surfactant proteins (Clark and Reid 2003). There are important differences in the approach and outcomes during mechanical ventilation of the term and preterm neonates. The mature term neonatal lung is less vulnerable to trauma and damage during mechanical ventilation and exposure to high concentrations of inspired oxygen. Preterm

birth is associated with interruption of normal in utero lung development, resulting in a simplified alveolar structure, immature breathing patterns and, in some instances, respiratory failure.

Northway and his colleagues in 1967 first examined the lung damage that occurred in infants with respiratory failure who were mechanically ventilated and coined the term bronchopulmonary dysplasia (BPD) to describe their findings (Northway et al. 1967). Dysplasia indicated the impaired development that occurred after damage and trauma to vulnerable immature lungs. The repeated opening and closing of the alveoli (atelectrauma) at high pressures (barotrauma) and high volumes (volutrauma) in the context of high concentrations of oxygen (chemotrauma) caused cystic and fibrotic changes within the neonatal lung. Coupled with increased risks of infection and inflammation (biotrauma), this led to the development of BPD. BPD had significant short- and long-term implications for respiratory mortality and morbidity (Ambalavanan and Carlo 2006) and occurred in infants of moderate preterm gestation (28 weeks and above) and whose birth weights were in excess of 1,400 g (Mammel and Bing 1996).

The nature of BPD has changed over time. Whereas the ‘old BPD’ was associated with inflammation and severe alveolar septal fibrosis (Husain et al. 1998; Lindroth et al. 1980), the ‘new BPD’ is associated with impaired alveolar growth alongside abnormal vascularisation in addition to interstitial fibrosis of the lungs (Mahut et al. 2007). The risk of improper lung repair in the new BPD is associated with the degree of prematurity, lower birth weight and increasing exposure to supplemental oxygen and mechanical ventilation (Mahut et al. 2007). The change in epidemiology and definition of BPD is attributable to advances in neonatal care and treatment over the past four decades, including the introduction of gentler ventilation techniques (such as permissive hypercapnia), antenatal corticosteroids, exogenous surfactant and changes in attitudes to the viability of very preterm neonates (Mammel and Bing 1996; Allen et al. 2003;

de Kleine et al. 1990; De Paepe et al. 2006; Donn and Sinha 2003). Despite improvements in the management of infants with respiratory distress syndrome (RDS) (sometimes also called hyaline membrane disease), BPD is still a major cause of morbidity in mechanically ventilated preterm neonates (Eber and Zach 2001; Hofhuis et al. 2002).

Not all infants who receive mechanical ventilation and supplemental oxygen are very preterm or of very low birth weight (VLBW, <1,500 g). Infants born at term or near-term may also develop respiratory failure from other causes, such as pneumonia (and sepsis), lung hypoplasia, aspiration (e.g. meconium aspiration syndrome), persistent pulmonary hypertension of the neonate, congenital diaphragmatic hernia or congenital heart disease (Allen et al. 2003; Eber and Zach 2001; Narang et al. 2008). The ventilation strategies employed for these conditions may be different, but the risk of ventilator-induced lung damage is ever present.

63.2 Short-Term Effects on Respiratory Function

Respiratory morbidity is common in infants who have been treated with mechanical ventilation and oxygen therapy for respiratory failure, especially in those who develop BPD (De Paepe et al. 2006; Bancalari and Claure 2008; Caudri et al. 2007). The infant moves from RDS to BPD as the effects of inflammation, mechanical ventilation-induced volutrauma and oxygen (chemotrauma) lead to chronic lung injury and repair. This pattern of injury and repair will eventually overshadow the effects of prematurity and growth restriction alone (Ambalavanan and Carlo 2006; Cook et al. 1996; Dani et al. 2006; Hutchison and Bignall 2008; Jobe and Ikegami 1998). It is still unclear what relative contribution mechanical ventilation and the underlying disease make to the pattern of lung injury seen in BPD especially since the need for mechanical ventilation is a marker for underlying disease severity (Claure and Bancalari 2008).

When considering short-term outcomes such as hospitalisation, infection, wheezing and the results of lung function tests, it is important to remember that BPD is a broad term whose definition and epidemiology has changed significantly over the past four decades (Eber and Zach 2001). For instance, the use of exogenous surfactant and antenatal corticosteroids alongside improvements in mechanical ventilation and oxygen therapy in the early 1990s has dramatically improved survival rates and reduced lung injury amongst those neonates who are born preterm, at very low birth weights or extremely low birth weights (Allen et al. 2003; Doyle 2008; Gerstmann et al. 1996). Moreover, the complexity of the change in BPD definition over time is added to by the observation that lung function testing not only examines the effects of mechanical ventilation on the lung but also looks at what influence the posthospital environment, which may include repeated respiratory infection and cigarette smoke, will have on lung development (Allen et al. 2003; Eber and Zach 2001).

During the first few years following discharge from hospital, children with BPD may have a prolonged requirement for supplemental oxygen and are more likely to be treated for pneumonia and be readmitted to hospital for respiratory infections, such as respiratory syncytial virus (RSV)-induced bronchiolitis (Allen et al. 2003; de Kleine et al. 1990; Baraldi and Filippone 2007; de Mello et al. 2006; Gross et al. 1998; Hjalmarson and Sandberg 2002; Kitchen et al. 1992; Marlow et al. 2006; Thomas et al. 2004). These young infants are reported to have higher incidences of wheezing, 'asthma-like' symptoms, hyperreactivity of their airways and increased levels of inflammatory markers (Baraldi and Filippone 2007; Thomas et al. 2004; Attar and Donn 2002; Hennessy et al. 2008). By the time these infants have reached school age, their risk of hospital admission is comparable to those children without a history of mechanical ventilation or BPD. There are conflicting reports as to whether there is an increased (McLeod et al. 1996; Ng et al. 2000; Siltanen et al. 2004) or the

same incidence (Kitchen et al. 1992; Northway et al. 1990) of asthma in ELBW/preterm survivors. Other studies suggest that reduced airway function in the first year of life may lead to transient wheeze but no long-term risk of atopy (Martinez et al. 1995).

Lung function measurements in infants are currently restricted to specialist laboratories. Those researchers who have performed measurement of pulmonary function in infants with BPD have shown reductions in lung volumes, impaired ventilation distribution, reduced dynamic compliance, increased airways resistance, evidence of air trapping and reduced expiratory flows compared with contemporaneous individuals and control subjects (Anand et al. 2003; Doyle et al. 1999, 2006; Hakulinen et al. 1996; Jacob et al. 1998; Kulasekaran et al. 2007). These values, although abnormal on many occasions, do not always fall within clinically significant ranges. This may reflect the differing aetiologies and definitions employed to describe BPD (Chan et al. 1989). There is currently much debate and investigation as to whether these abnormalities track into adolescence and adulthood (Doyle et al. 1999, 2006; Blayney et al. 1991; Filippone et al. 2003; Koumbourlis et al. 1996).

63.3 Long-Term Effects on Respiratory Function

BPD is a major cause of long-term respiratory morbidity in adolescents and adults who were ventilated as neonates with respiratory failure. There are many cross-sectional studies investigating respiratory outcome in these individuals who have shown increased prevalence of airflow obstruction, air trapping (hyperinflation and/or loss of lung elasticity) and impairments in the gas exchange properties of the lung, as shown in Table 63.1 (Doyle et al. 1999, 2006; Jacob et al. 1998; Kulasekaran et al. 2007; Pelkonen et al. 1998). Other researchers show no significant differences between those who received assisted ventilation and those who did not (Table 63.1) (Anand et al. 2003; Hakulinen et al. 1996).

Table 63.1 Cross-sectional lung function data from studies of mechanically ventilated survivors, including some with BPD

Authors (cohort years of birth)	Age (years)	Mechanical ventilation	Controls	Results
Kulasekaran et al. (1989–1990) (2007)	7–10	<i>n</i> = 47 MV: 10 (7–18) ^a	45 PTC	↓ FEF _{25–75} (70.1 ± 24.5 % ^c), no significant BD (61.7 % MV versus 47.7 % PTC) No significant difference in FEV ₁ (−5.1 % [−10.5 to 0.4 %] ^b), FVC (−3.5 % [−8.8 to 1.8 %] ^b), DL _{CO} (−3.4 % [−8.8 to 7.8 %] ^b) between those MV and not, reduced compared to predicted values (FEV ₁ 82.3 ± 13.9 % ^c , FVC 88.7 ± 13.5 % ^c , DL _{CO} 79.2 ± 13.8 % ^c)
Doyle et al. (1977–1982) (1999, 2006)	8	<i>n</i> = 33 with BPD MV: 2 (0–6)	114 PTC	Airway obstruction ↓ FEV ₁ (80.4 ± 15.9 % ^c), FEF _{25–75} (65.4 ± 27.2 % ^c) Evidence of hyperinflation/loss of lung elasticity ↑ RV/TLC (37.3 ± 11.1 % ^d)
Jacob et al. (1981–1987) (1998)	10.6 (1.7) ^b	<i>n</i> = 15 MV: 56 (22–77) ^a	15 PTC	Airway obstruction ↓ FEV ₁ (63.6 ± 20.6 % ^c), FEF _{25–75} (40.3 ± 24.5 % ^c), FEV ₁ /FVC (69.2 % ± 9.0 ^b); evidence of hyperinflation/loss of lung elasticity ↑ RV/TLC (181.8 ± 84.3 % ^c); DL _{CO} reduced compared with predicted values (83.4 ± 10.5 % ^c)
Anand et al. (1980–1981) (2003)	15	<i>n</i> = 83 MV: no details	45 PTC	Normal results, no influence of neonatal mechanical ventilation on lung function outcome (FEV ₁ 94.1 ± 14.9 % ^c , FEF _{25–75} % 87.6 ± 26.9 % ^c)
Northway et al. (1964–1973) (1990)	18.3 (2.7) ^b	<i>n</i> = 26	26 PTC	Airway obstruction ↓ FEV ₁ (74.8 ± 2.9 % ^c , FEF _{25–75} % 46.5 ± 3.6 % ^c) Evidence of airway hyperreactivity; evidence of hyperinflation/loss of lung elasticity ↑ RV/TLC (121.9 ± 7.2 % ^c)
Doyle et al. (1977–1982) (1999, 2006)	18.9 (1.1) ^b	<i>n</i> = 33 with BPD MV: 2 (0–6)	114 PTC	Airway obstruction ↓ FEV ₁ (81.6 ± 18.7 % ^c), FEV ₁ /FVC (73.9 ± 12.9 % ^d), FEF _{25–75} % (57.5 ± 25.7 % ^c)

MV mechanically ventilated, PDA patent ductus arteriosus, NBW normal birth weight, NTC normal term controls, PTC preterm controls (no BPD), RFT respiratory function tests, PD₂₀ methacholine bronchoprovocation test, EIB exercise-induced bronchoconstriction, BD bronchodilation, AHR airway hyperreactivity, PEF peak expiratory flow, FEV₁ forced expiratory volume in 1 s, FVC forced vital capacity, FEF₂₅ %, FEF₅₀ %, FEF₇₅ %, FEF_{25–75} % (forced expiratory flows at 25, 50, 75 % and from 25 to 75 % of FVC), TLC total lung capacity, RV residual volume, DL_{CO} diffusing capacity of the lung for carbon monoxide

^aMedian number of days (interquartile range)

^bMean (standard deviation)

^cPercent predicted mean ± standard deviation

^dMean ± standard deviation

^eMean difference (95 % confidence interval)

Few studies report findings from the same individuals who were mechanically ventilated as a neonate and developed BPD through to late adolescence or adulthood. Those studies that do report three significant findings: Firstly, airflow obstruction is a consistent feature of respiratory function in survivors of BPD. For instance, mean forced expiratory volume in one second (FEV_1) has been reported to be reduced at 2 years of age whilst forced mid-flow values ($FEF_{25-75\%}$) were less than predicted at 2, 7, 8 and 10 years of age (Blayney et al. 1991; Filippone et al. 2003). Moreover, reduced maximal flows at functional residual capacity in children at 2 years of age were predictive of reduced $FEF_{25-75\%}$ at 8 years of age (Filippone et al. 2003). Secondly, airflow obstruction appeared to improve in some cases over time. Blayney reported that 59 % of the patients with an FEV_1 below 80 % predicted at 7 years of age had increased FEV_1 % predicted at 10 years (Blayney et al. 1991), although this improvement may have just reflected regression towards the mean, rather than true improvement. In another study Doyle and colleagues reported an increase in FEV_1 and $FEF_{25-75\%}$ between the ages of 8 and 14 years in a cohort of infants of birth weight <1,501 g (Doyle et al. 1999). Moreover, a number of groups have reported an improvement in the ratio of residual volume (Hakulinen et al. 1996) to total lung capacity (TLC) suggesting that air trapping and/or lung elasticity improves in the teenage years (Doyle et al. 1999; Koumbourlis et al. 1996). There is a suggestion that airway hyperreactivity may contribute to chronic airflow obstruction in those individuals who received mechanical ventilation and developed BPD (Koumbourlis et al. 1996). Of those who had assisted ventilation, a high percentage had reduced FEV_1 (mean 87.9 % SD 18.3 % predicted) and $FEF_{25-75\%}$ (mean 62.3 %, SD 29.0 % predicted) that responded to bronchodilator therapy, and a further half of these cases responded to a histamine airway challenge (Koumbourlis et al. 1996). Thirdly, despite the improvement in lung function over the teenage years, some respiratory impairment persists in adults who had previously had BPD as an infant. For instance, 19-year-olds who had previously

had BPD were found to have a mean difference in FEV_1 of -11.3 % predicted (-16.9 to -5.7 %, $p < 0.001$) compared with controls who had not received assisted ventilation and did not develop BPD (Doyle et al. 2006). Moreover, Doyle and colleagues found that individuals who received mechanical ventilation and developed BPD may have lung function, as measured by the ratio of FEV_1 to forced vital capacity (FVC), that is declining at a faster rate compared with a control group who had received less mechanical ventilation and did not develop BPD (Doyle et al. 2006).

A number of neonatal variables have been associated with abnormal respiratory function later in life. Early gestational age at birth has been associated with worse airflow as measured by the FEV_1 ($r = 0.788$, $p < 0.01$) and the $FEF_{25-75\%}$ ($r = 0.745$, $p < 0.01$) (Bader et al. 1987). Moreover, the total duration of ventilation was negatively associated with abnormal air flow as measured by the FEV_1 ($r = -0.763$, $p < 0.01$), FVC, $FEF_{50\%}$ and $FEF_{25-75\%}$ (Bader et al. 1987; Pelkonen et al. 1997). However, neither birth weight nor duration of oxygen supplementation correlated with resting lung function and none of these variables was associated with exercise performance as measured by peak oxygen consumption, even though exercise performance does not correlate with resting pulmonary function, as discussed later.

63.4 Long-Term Effects on Exercise Capacity

The prevalence of exercise-related morbidity such as cough, dyspnoea and wheeze is significantly higher in individuals who were mechanically ventilated as neonates and developed BPD (Doyle 2008; Gross et al. 1998; Bader et al. 1987; Kriemler et al. 2005; Vrijlandt et al. 2006). These cardiopulmonary limitations may not be evident at rest using standard respiratory function measurements but only become apparent when the respiratory and cardiac systems are put under stress during an exercise test (Doyle 2008; Gross et al. 1998; Bader et al. 1987; Kriemler et al. 2005; Vrijlandt et al. 2006; Narang et al. 2006). Many of the studies investigating these cardiopulmonary

outcomes have used different methods of exercise testing, incorporating different protocols and work intensities, and have therefore displayed conflicting data (Doyle 2008; Gross et al. 1998; Bader et al. 1987; Kriemler et al. 2005; Vrijlandt et al. 2006; Narang et al. 2006; Baraldi et al. 1991; Jacob et al. 1997; Kilbride et al. 2003; Pianosi and Fisk 2000; Santuz et al. 1995). However, most studies describe ventilatory limitation of varying degrees. Some neonatal survivors with BPD demonstrate compensatory alterations in the ventilation strategy to achieve peak oxygen consumption close to predicted (Table 63.2) (Doyle 2008; Gross et al. 1998; Bader et al. 1987; Kriemler et al. 2005; Vrijlandt et al. 2006; Narang et al. 2006; Baraldi et al. 1991; Jacob et al. 1997; Kilbride et al. 2003; Pianosi and Fisk 2000; Santuz et al. 1995). The maximum rate of oxygen consumption during peak exercise in the mechanically ventilated BPD survivors is reduced on many occasions when compared with control groups, but does not often fall into clinically significant ranges (Table 63.2) (Doyle 2008; Bader et al. 1987; Kriemler et al. 2005; Vrijlandt et al. 2006; Narang et al. 2006; Baraldi et al. 1991; Jacob et al. 1997; Kilbride et al. 2003; Pianosi and Fisk 2000; Santuz et al. 1995). When investigating airway hyperreactivity or exercise-induced bronchoconstriction, many of the researchers have found a higher incidence in preterm survivors who received mechanical ventilation and oxygen supplementation for respiratory failure as neonates; see Table 63.2 (Doyle 2008; Gross et al. 1998; Bader et al. 1987; Kriemler et al. 2005; Vrijlandt et al. 2006; Narang et al. 2006; Baraldi et al. 1991; Jacob et al. 1997; Kilbride et al. 2003; Pianosi and Fisk 2000; Santuz et al. 1995). However, since the aetiology of mechanical ventilation-induced airway hyperreactivity and bronchoconstriction is poorly understood, it is difficult to gauge the degree to which genetic and immunological factors play a part (Doyle 2008; Gross et al. 1998; Bader et al. 1987; Kriemler et al. 2005; Vrijlandt et al. 2006; Narang et al. 2006; Baraldi et al. 1991; Jacob et al. 1997; Kilbride et al. 2003; Pianosi and Fisk 2000; Santuz et al. 1995).

63.5 Effects on Other Aspects of Respiratory Health

The use of mechanical ventilation and oxygen supplementation in neonates suffering respiratory failure has life-long morbidity implications, with higher rates of respiratory morbidity such as wheeze, cough, asthma and repeated respiratory infection (Table 63.3) (Caudri et al. 2007; Gross et al. 1998; Broughton et al. 2007). This respiratory morbidity places a burden on the children, their families and healthcare systems. Whilst wheeze and respiratory infection appear to be common complaints in infants and younger children, there is a decline in these symptoms as the children age (Caudri et al. 2007; Broughton et al. 2007). However, cough is a consistent symptom throughout childhood and adolescence. Asthma and cigarette smoke exposure either before or after birth both compound the respiratory morbidity experienced. Other researchers have found no significant differences in respiratory health between individuals who were ventilated as neonates (Kulasekaran et al. 2007; Vrijlandt et al. 2006; Doyle et al. 2001). More research is needed on geographical cohorts for a definitive answer.

63.6 Neurodevelopmental Outcomes

Survivors of mechanical ventilation with the classical scarring and cystic type of BPD who were born in the 1970s and early 1980s had poor neurodevelopmental outcomes, as well as abnormal lung function (Northway et al. 1990), compared with preterm controls without BPD (Saigal and O'Brodovich 1987). Neurosensory problems also occur more frequently in preterm survivors with the 'new BPD' compared with preterm survivors without BPD (Anderson and Doyle 2006). Some of the specific neurodevelopmental outcomes have been recently reviewed (Anderson and Doyle 2006) and are summarised as follows.

Table 63.2 Cross-sectional exercise test data from studies of mechanically ventilated survivors, including some with BPD

Authors (cohort years of birth)	Age (years)	MV	Controls	Ergometer	Results
Gross et al. (1985–1986) (1998)	7	<i>n</i> = 43 MV: median 34 days	53 PTC 108 NBW	Treadmill	No difference in VO_{2peak} (41.1 ± 7.5 versus NBW 43.2 ± 8.6 mL/min/kg ^b), HR_{peak} (192 ± 14 versus 199 ± 10 beats/min), $\uparrow$ EIB ($FEV_1 < 80\%$ postexercise in 54 % versus 17 % of NBW ^b)
Pianosi et al. (1986–1987) (2000)	8–9	<i>n</i> = 32 MV: 19 (3–120) ^a	15 NBW	Cycle	$\uparrow$ RR ($p = 0.005$), no increase in VT ($p = 0.2$), $\downarrow$ VO_{2peak} (41 ± 8 versus NBW 46 ± 8 mL/min/kg, $p < 0.05$)
Bader et al. (1973–1979) (1987)	10.4 (0.6) ^c	<i>n</i> = 10 MV or O ₂ : ≥ 30 days	8 NBW	Treadmill	No difference in VO_{2peak} (39.1 ± 3.7 versus 43.0 ± 3.8 mL/min/kg ^c), $\downarrow$ V_E ($p < 0.02$), $\downarrow$ SpO ₂ ($p < 0.05$), $\uparrow$ transcutaneous carbon dioxide ($p < 0.05$), $\uparrow$ EIB (50 % versus 0 % NBW)
Jacob et al. (1981–1987) (1997)	10.6 (1.7) ^b	<i>n</i> = 30 MV: 56 (21–77) ^a	13 NBW	Cycle	No difference in VO_{2peak} (36.1 ± 7 versus NBW 37.9 ± 5.3 mL/min/kg ^b), less respiratory reserve ($\uparrow$ V_E/MVV , 96.5 ± 15 versus NBW 65.2 ± 14.5 % of predicted)
Santuz et al. (1981–1987) (1995)	6–12	<i>n</i> = 12 MV: 20 ± 15 (7–60) ^a	16 NBW	Treadmill	$\downarrow$ VO_{2peak} (25.2 ± 10.3 versus NBW 37.1 ± 10.4 mL/min/kg ^b , $p < 0.01$), $\downarrow$ V_E (20.8 ± 9.8 versus NBW 30.7 ± 7.9 L/min ^b , $p < 0.01$), $\uparrow$ RR ($p < 0.001$), $\uparrow$ EIB (FEV_1 postexercise $-8 \pm 6\%$ versus $-2 \pm 1\%$ NBW, $p < 0.01$)
Kilbride et al. (1983–1989) (2003)	9–15	<i>n</i> = 50 MV: 33 ± 20 (0–78) ^a	25 NBW	Treadmill	$\downarrow$ VO_{2peak} (29.0 ± 5.9 versus 38.5 ± 5.2 mL/min/kg, $p < 0.001$)
Vrijlandt et al. (1983) (2006)	19	<i>n</i> = 44 MV: 6.3 ± 12 (0–51)	48 NBW	Cycle	No difference in VO_{2peak} (35.3 ± 6.9 versus NBW 37.4 ± 6.3 mL/min/kg), $\downarrow$ V_E (70.0 ± 17.9 versus NBW 80.9 ± 20.8 L/min, $p = 0.011$), asthma prevalence low (2 % versus NBW 0 %)

NS no significant, *MV* mechanical ventilation days, *NBW* normal birth weight, *EIB* exercise-induced bronchoconstriction/airway hyperreactivity, *VO₂* oxygen consumption, *VO_{2peak}* oxygen consumption at peak exercise, *V_E* ventilation rate at peak exercise, *MVV* maximum voluntary ventilation, *RR* respiratory rate, *HR_{peak}* heart rate at peak exercise, *W_{max}* load (watts) at peak exercise, *FEV₁* forced expiratory volume in one second, *VT* tidal volume, *SpO₂* oxygen saturation

^aMedian number of days (interquartile range)

^bMean and standard deviation

^cMean and standard error of the mean

Table 63.3 Respiratory morbidity for mechanically ventilated neonates as they age

Authors (cohort years of birth)	Age (years)	Mechanical ventilation	Controls	Methods	Results
Broughton et al. (1998–2003) (2007)	1	<i>n</i> = 111 MV: 13 (4–29) ^b	0 NBW	Questionnaire Diary cards	60/111 (54 %) reported wheeze, had history of longer duration of mechanical ventilation, lower birth weight, lower gestational age, BPD and family history of atopy
Gross et al. (1985–1986) (1998)	7	<i>n</i> = 43 MV: 34	53 PTC 108 NBW	Clinical exam	Increased incidence of wheeze, chronic cough and use of bronchodilators
Jacob et al. (1981–1987) (1998)	10.6 (1.7) ^d	<i>n</i> = 15 MV: 56 (22–77) ^b	15 PTC	Questionnaire (IUATLD)	Increased exercise morbidity, dyspnoea, use of inhaled medication compared with control
Kulasekaran et al. (1989–1990) (2007)	7–10	<i>n</i> = 47 MV: 10 (7–18) ^b 'New BPD'	45 PTC	Clinical exam	No significant difference between groups in incidence of asthma, wheeze, allergies, family history of asthma or atopy
Pelkonen et al. (1983–1987) (1998)	7–12	<i>n</i> = 40 <i>n</i> = 17 MV: 7 (1–85) ^c <i>n</i> = 14 MV: 8 (1–165) ^c <i>n</i> = 9 MV: 14 (1–80) ^c	20 NBW	Questionnaire Clinical exam	27/40 (67.5 %) had respiratory symptoms (^b asthma, dyspnoea and chronic cough)
Vrijlandt et al. (1983) (2006)	19	<i>n</i> = 42 MV: 6.3 (0–51) ^c	48 NBW	Questionnaire	No significant differences, some increase noted in smoking rates
Wong et al. (1980–1987) (2008)	19 (17–33) ^d	<i>n</i> = 21 MV: 38 (9–135) ^c	0 NBW	Clinical exam	Persistent respiratory symptoms, wheeze, cough and dyspnoea reported in 71 % of subjects; 14 % used inhaled medication

This sample of authors does not represent all published data regarding respiratory morbidity and mechanical ventilation; it is intended as an overview
IUATLD International Union Against Tuberculosis and Lung Disease bronchial symptoms questionnaire, *AHR* airway hyperresponsiveness

^aDoctor diagnosed plus use of inhaled medication

^bMedian number of days (interquartile range)

^cMedian number of days (range)

^dMean (SD)

63.6.1 Neurosensory Problems

Cerebral palsy occurs more frequently in children with BPD; 15 % had cerebral palsy in one study of very low birth weight (VLBW, birth weight <1,500 g) survivors with BPD compared with 3–4 % of controls (Skidmore et al. 1990). In a more recent study, BPD was a significant risk factor for cerebral palsy at 18–22 months' corrected age in a study of 827 infants <25 weeks born between 1993 and 1999 (Hintz et al. 2005). Apart from cerebral palsy, some infants with BPD have been described to have a specific movement disorder affecting the limbs, neck, trunk and oral-buccal-lingual movements (Perlman and Volpe 1989), and they also exhibit poorer fine and gross motor skills than VLBW children without BPD (Short et al. 2003; Vohr et al. 1991). BPD is also associated with more visual (McGinnity and Halliday 1993) and auditory problems (Gray et al. 2001) although the degree of impairment is often not sufficiently severe to either meet the definition of legal blindness or require correction of deafness with hearing aids or cochlear implants.

63.6.2 General Cognitive Functioning

Rates of cognitive and motor delay in a large cohort of VLBW preschoolers with BPD were more than double that of VLBW peers without BPD (Singer et al. 1997). In general, school-aged children with BPD have lower IQs than VLBW children without BPD (Short et al. 2003; Gray et al. 2004; Hughes et al. 1999; O'Shea et al. 1996; Robertson et al. 1992; Taylor et al. 1998), although some studies have failed to find significant differences between groups (Vohr et al. 1991; Bohm and Katz-Salamon 2003).

63.6.3 Other Neurological and Cognitive Areas

In one study of VLBW children, 59 % who had BPD had problems with attention compared with

32 % in controls (Farel et al. 1998). In another study the rate of attention deficit hyperactivity disorder in 8-year-old VLBW children with BPD was 15 %, double that of non-BPD VLBW children (Short et al. 2003). Speech and language disorders are more common in preterm children with BPD (Casiro et al. 1990). In one study 15 % of children with BPD had a significant receptive language impairment, and 9 % had a significant expressive language impairment, more than double that of non-BPD VLBW peers (Lewis et al. 2002). Approximately 50 % of school-aged VLBW children with BPD were enrolled in speech-language therapy in one study, in contrast with about 20 % of VLBW children without BPD (Short et al. 2003; Lewis et al. 2002).

A number of studies have found that children with BPD perform significantly below controls on the Developmental Test of Visual-Motor Integration (Gray et al. 2004; Hughes et al. 1999; Robertson et al. 1992), suggesting visual-spatial perceptual deficits. In a longitudinal study by Taylor and colleagues (1998, 2004), school-aged children with BPD had a specific impairment on perceptual motor tasks (Taylor et al. 1998), whilst a later follow-up (at a mean age of 16 years) revealed that weeks of oxygen requirement was strongly associated with worse performance on a number of measures that assess visual-spatial perceptual skills (Taylor et al. 2004).

Children with a history of BPD have more school-based problems than those without BPD (Vohr et al. 1991). In one study children with BPD performed significantly below VLBW children without BPD and full-term controls on tests of reading and mathematics (Hughes et al. 1999), and in another study the rate of problems in reading and mathematics was reported to be as high as 47 % (Farel et al. 1998). Poorer spelling skills have also been reported in school-aged children with BPD (Robertson et al. 1992). Children with BPD are more likely to require educational assistance (Vohr et al. 1991; Farel et al. 1998), with 54 % of children with BPD enrolled in special education classes compared with 37 % of controls in one study (Short et al. 2003).

Preterm children with BPD exhibit more behavioural problems than peers without BPD. In

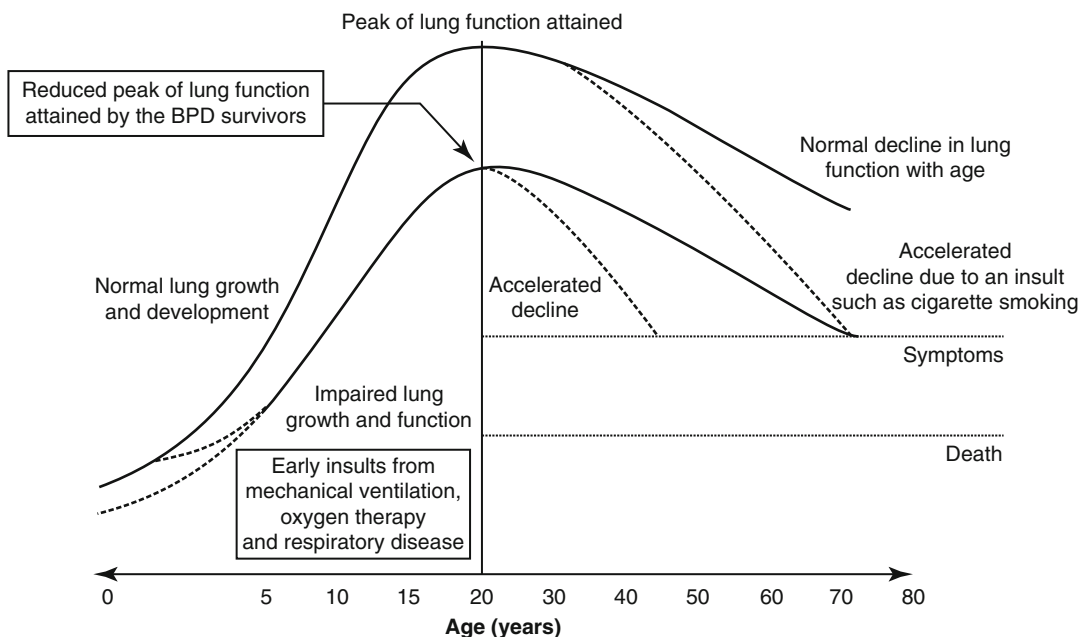


Fig. 63.1 Schematic representing normal lung development and normal decline in lung function compared with abnormal or impaired development that may occur

after mechanical ventilation and oxygen therapy and development of BPD

a recent study BPD children scored worse than classroom controls on several aspects of behaviour, including internalising behaviours and inattention.

63.7 Future Perspectives

Mechanical ventilation is unlikely to be the single cause of the development of BPD in neonates. The treatment of RDS with assisted ventilation may commit patients to a vicious cycle of iatrogenic lung injury which leads to worsening disease, further respiratory compromise, incomplete repair and therefore prolonged need for mechanical ventilation (Eber and Zach 2001; Narang et al. 2008; Claure and Bancalari 2008; Doyle 2008; Wong et al. 2008).

In keeping with the fetal origins of adult disease hypothesis, there have been reports of birth weight being a determinant of lung function (Lawlor et al. 2005). Similarly, there is concern amongst researchers that the abnormal lung function seen in survivors of mechanical ventilation

who develop BPD may result in chronic diseases of adulthood (Baraldi and Filippone 2007; Doyle et al. 1999, 2006; Blayney et al. 1991; Filippone et al. 2003; Koumbourlis et al. 1996).

Normal lung growth increases from birth until approximately 20 years of age when the peak in lung function occurs, which is then followed by a natural decline as individuals age (Fig. 63.1). Insults such as preterm birth and infection may lead to arrested lung growth and development. Other early insults such as mechanical ventilation-induced atelectrauma, barotrauma and volutrauma may lead to further damage and interfere with lung growth and development. Abnormal lung growth and development in turn could result in a reduced peak lung function as an individual reaches early adulthood. If further damage to the lungs occurs from an external insult, such as cigarette smoking, the natural decline in lung function may be accelerated. This may lead to accelerated decline and earlier presentation to adult physicians with symptoms that may mimic smoking-related disease such as COPD. Those who had the most protracted lung disease as

infants (i.e. BPD) should be advised to avoid cigarette smoke.

Chronic obstructive pulmonary disease (COPD) and emphysema are common diseases in adult respiratory medical practice. COPD and emphysema are disease processes related to smoking, severe asthma or chronic infection and result in destruction of alveolar walls. BPD is the result of disruption in development of alveolar walls and may mimic the symptoms of COPD as the populations of mechanically ventilated neonates progress through adulthood (Narang et al. 2006; Wong et al. 2008; Thébaud and Abman 2007). Since the cohort first described by Northway are now in their 40s, respiratory physicians in adult medicine must increasingly be aware of perinatal history and investigate a differential diagnosis for those young adults presenting with emphysema (Wong et al. 2008). Neonates who receive mechanical ventilation and oxygen therapy should be followed into adulthood to further classify outcomes and provide information for differential diagnoses.

Despite the concerns about the long-term effects of mechanical ventilation, it is clear that the short-term respiratory outcomes of neonates treated with assisted ventilation have improved over time and more particularly with the advent of altered ventilation strategies, such as permissive hypercapnia, antenatal corticosteroids and postnatal surfactant treatment. The magnitude of the impairment found in survivors after mechanical ventilation can be significant, but most are able to live normal lives. With improvements to existing treatment and new treatments implemented in the future, we may expect further improvements in long-term respiratory health and neurological function in the years to come.

Essentials to Remember

Compared with preterm children who do not require mechanical ventilation, survivors of neonatal mechanical ventilation, particularly those who develop BPD, have:

- More prolonged oxygen dependency and readmissions to hospital in the first few years after discharge
- More airway obstruction
- Diminished exercise tolerance
- Higher rates of asthma and other respiratory symptoms
- More adverse neurological outcomes

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Stacey L. Valentine and Adrienne G. Randolph

Educational Goals

- To identify the short- and long-term outcomes of mechanical ventilation
- To understand the scales used to measure short- and long-term outcomes in critically ill children
- To understand the effects of mechanical ventilation on long-term respiratory function
- To recognize the effects of mechanical ventilation on neuromuscular function
- To identify the psychological sequelae of mechanical ventilation
- To understand the effects of mechanical ventilation on other aspects of quality of life

those children who survive critical illness. Critical illness affects many domains of the developing child, including physical, psychological, neurocognitive, and social development. It also has a significant impact on the quality of life of the family unit. Because of the normal and broad variability that occurs during normal child development, it is challenging to assess the long-term outcomes after recovery from critical illness in children. Given that most children survive their episode of acute respiratory failure, methods to measure the long-term effects of critical illness and mechanical ventilation in children are essential.

Assessment of global impairment following mechanical ventilation is complicated by patient heterogeneity from factors including age (infant to adolescent) and underlying health conditions (chronic neurologic, pulmonary and cardiac disease, etc.). It is clear that increased severity of illness, PICU LOS, and admission diagnosis are associated with worsened outcomes (Fiser 1992; Fiser et al. 2000; Randolph 2009; Ruttimann et al. 1996). In adults, the major long-term consequences of lung injury are related to neuromuscular, cognitive, and psychological dysfunction rather than pulmonary dysfunction (Rubenfeld and Herridge 2007). In children, mechanical ventilation can impact a child's development and their pulmonary and neuromuscular function as well as result in cognitive and psychological impairments. This chapter will review what is known about the short- and long-term effects of mechanical ventilation on the developing child.

64.1 Introduction

As pediatric intensive care unit (ICU) survival increases, it becomes increasingly important to consider the short- and long-term outcomes of

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Table 64.1 Comparison of severity of illness and organ dysfunction scores in the PICU

	PRISM III	PIM II	PELOD
Predicted outcome	Mortality	Mortality	Morbidity
Timing of measurement	1st 24 h of PICU admission	1st hour of PICU admission	Daily
Variables measured	Temperature Heart rate Systolic blood pressure Acidosis pH CO ₂ PaCO ₂ PaO ₂ Glasgow Coma Scale Pupillary reflexes Potassium Glucose Blood urea nitrogen Creatinine White blood count PT/PTT Platelets	Heart rate Systolic blood pressure Mechanical ventilation PaO ₂ Pupillary reflexes Admission criteria High- vs. low-risk diagnoses	Heart rate Systolic blood pressure Mechanical ventilation PaCO ₂ PaO ₂ /FiO ₂ Glasgow Coma Scale Pupillary reflexes SGOT Creatinine White blood count PT/PTT Platelets

PRISM III Pediatric Risk of Mortality, *PIM II* Pediatric Index of Mortality, *PELOD* Pediatric Logistic Organ Dysfunction

64.2 Short-Term and Long-Term Outcome Measures

Short-term outcome measures are those evaluated during the pediatric ICU stay and/or hospital stay. Longer-term outcome measures are those that are measured after hospital discharge and/or are permanent. Mortality is the most commonly measured ICU outcome and is influenced by the initial severity of illness of the patient. Lacroix et al. in 2005 performed a study to evaluate the best tools available to estimate severity of illness in critically ill children. They found the Pediatric Risk of Mortality III (PRISM III), Pediatric Index of Mortality 2 (PIM II), and Pediatric Logistic Organ Dysfunction (PELOD) scores to all be valid but to have different strengths and weaknesses.

The variables included in the PRISM III, PIM II, and PELOD scores differ because the scores assess different outcomes (see Table 64.1). The PRISM III score quantifies the mortality risk of a

child using “the worst” laboratory, clinical, and physiologic values during the first 24 h of admission (Pollack et al. 1996, 1988). The Pediatric Index of Mortality (PIM) quantifies mortality risk based on five physiologic variables obtained within the first hour of ICU admission plus three nonphysiologic baseline variables (Shann et al. 1997). The PRISM III and PIM II scores are validated for use as mortality outcome predictors across groups of patients. They are not designed to prognosticate in individual patients. Both PRISM III and PIM II are used nationally in the USA to benchmark ICU performance for patients in medical-surgical ICUs (Czaja et al. 2011). The Pediatric Logistic Organ Dysfunction (PELOD) score (Le Gall et al. 1996; Marshall et al. 1995; Vincent et al. 1996; Proulx et al. 1996; Leteurtre et al. 1999) is the only multiple organ dysfunction score validated across more than one pediatric ICU. PELOD measures 12 variables at six levels of dysfunction. The worst PELOD during ICU admission has been used as a measurement

of the worst illness severity. The change in PELOD (delta PELOD) has been used to assess whether a patient improves or worsens over a specified time period.

64.2.1 Mortality

The mortality rates for critically ill patients vary depending on the population studied. In the USA mortality rates for patients in mixed medical-surgical ICUs are reported as 2.8–6 % in critically ill children compared to 10–30 % in critically ill adults. While international numbers are not readily available, in the USA, over 250,000 children ages 1–19 years each year receive ICU care and approximately 23–40 % of these children (Dahlem et al. 2003; Watson et al. 2002; Angus et al. 2001; Census 2002; Fedora et al. 2005) receive mechanical ventilator support. Of those children receiving mechanical ventilation, approximately 30–50 % were previously healthy (Watson et al. 2002). These numbers differ internationally. Fedora et al. (2005) found that 23 % of children admitted to the PICU in the Czech Republic received mechanical ventilator support. Of those children, the mortality rate was 3.5 %. The origin of respiratory failure was extrapulmonary in 66 % of the patients and only 19 % were chronically ill. The PRISM III scores and length of stay were twofold higher in mechanically ventilated patients than those not receiving mechanical ventilation. In developing nations, malnutrition and immune compromise from HIV influence the outcome of children who are mechanically ventilated.

In an international retrospective cohort study of 36 pediatric intensive care units across seven countries, Farias et al. (2006) identified factors that were associated with survival in pediatric patients receiving mechanical ventilation for more than 12 h. The 15.6 % of children who died had more severe lung disease on admission (higher peak inspiratory pressure and more severe hypoxemia) and higher overall illness severity (PRISM III score) and were more likely to

develop acute renal failure. Most of the children were mechanically ventilated for acute, emergent conditions, many of which were from severe infections or injury.

Given the heterogeneity of disease requiring acute mechanical ventilator support, it is useful to evaluate mortality rates of patients receiving mechanical ventilation based on their underlying disease process and degree of lung disease. Acute lung injury (ALI) and its more severe form acute respiratory distress syndrome (ARDS) are severe forms of respiratory failure occurring in 9 % (Dahlem et al. 2003; Watson et al. 2002; Angus et al. 2001) of mechanically ventilated children. ALI is a syndrome comprised of acute onset of severe hypoxia and bilateral lung infiltrates not caused by left heart failure. ALI has mortality rates of 8–18 % in nonimmune compromised patients and 40–80 % in children with underlying immune compromise (Randolph 2009; Zimmerman et al. 2010; Flori et al. 2005; Erickson et al. 2007). In Australia and New Zealand, Erickson et al. (2007) reported that ALI accounted for 30 % of the total PICU deaths. Mortality ranged from 44 to 80 % in patients with ARDS with a history of bone marrow transplantation in multiple studies (Randolph 2009). Factors that had an independent association with mortality were severity of illness, $\text{PaO}_2/\text{FiO}_2$ ratio, the presence of a non-pulmonary and non-CNS organ dysfunction, and the presence of CNS dysfunction (Randolph 2009; Flori et al. 2005; Erickson et al. 2007).

Severe asthma accounts for 2–20 % of adult ICU admissions. Nearly one third of adults with status asthmaticus require mechanical ventilation and 10–20 % of them will not survive. In contrast, less than 2 % of pediatric patients hospitalized for an asthma exacerbation require mechanical ventilator support, and mortality is rare (Chiang et al. 2009; Roberts et al. 2002). Bronchiolitis, a diagnosis occurring mostly in infancy, also has airway hyperinflation, mucous plugging, and bronchospasm. Mortality in otherwise healthy infants with bronchiolitis is also an uncommon event.

64.3 Affects of Mechanical Ventilation on Respiratory Function and the Upper Airways

Although mechanical ventilation can be lifesaving, complications from intubation and mechanical ventilation do occur in infants and children. Rivera and Tibballs (1992) found complications from intubation and mechanical ventilation occurred in 24 % of patients. These complications included infection (2.3 %), air leak (6.8 %), post-extubation stridor (2.4 %), bronchopulmonary dysplasia (2.3 %), and atelectasis (7.8 %). In 2007, Jorgenson et al. (2007) performed endoscopic airway evaluations on 1,435 intubated pediatric patients following extubation to determine the incidence of airway injury following intubation. Airway injuries were classified as minor, moderate, or severe. Ninety percent of patient had airway injury on endoscopic evaluation. Thirty-one percent of patients had vocal cord edema, 8.8 % had ulcerations of the arytenoids, 7.9 % had annular ulcerations in the subglottic region, 2.8 % had subglottic stenosis, 2 % had fibrous nodules on the vocal folds, and 0.45 % had vocal cord paralysis. In a study examining post-extubation complications in infants with bronchiolitis, immediate post-extubation complications including upper airway obstruction were common, and fortunately, long-term complications such as subglottic stenosis were very rare (Gomes Cordeiro et al. 2004).

64.3.1 Ventilator-Induced Lung Injury

Mechanical ventilation can also lead to ventilator-induced lung injury (VILI) which has been associated with morbidity and mortality in critically ill children. VILI is caused by trauma to the lungs from the pressures delivered by the ventilator. The pattern of lung injury that results from VILI resembles the early pattern of injury seen in ARDS (Pinhu et al. 2003). Higher ventilatory pressures lead to alveolar overdistention (volutrauma). Repetitive alveolar collapse and re-expansion can result in atelectrauma. Reducing

plateau pressure to ≤ 30 by targeting TV ≤ 6 /kg has decreased mortality in adults with ARDS (The Acute Respiratory Distress Syndrome Network 2000, 2004). In children, Farias et al. demonstrated a decreased mortality in patients receiving peak inspiratory pressures (PIP) ≤ 35 .

64.3.2 Ventilator-Induced Pneumonia

Ventilator-associated pneumonia (VAP) remains a complication of mechanical ventilation and has been associated with increased PICU length of stay, mechanical ventilator days, and mortality (Raymond and Aujard 2000; Bigham et al. 2009; Balcells Ramírez et al. 2004). In 2004, Balcells Ramírez et al. (2004) found that 17.4 % of mechanically ventilated children developed VAP in a prospective observational study evaluating the prevalence of mechanical ventilation in pediatric patients across 33 PICUs in Spain. VAP bundles have been implemented to reduce the incidence of ventilator-associated pneumonia. In 2009, Bigham et al. (2009) reported a reduction in the incidence of VAP rate from 5.6 to 0.3 infections per 1,000 ventilator days with the implementation of a VAP prevention bundle.

64.3.3 Respiratory Function

In studies looking at the long-term outcomes of adults surviving lung injury, the majority of adult patients who survive do not have long-term pulmonary dysfunction. Of those with respiratory dysfunction, there is significant variability in the number of patients with reduced diffusion capacity (33–82 %), obstructive defects (0–33 %), and restrictive defects (0–50 %) (Rubinfeld and Herridge 2007) necessitating comprehensive studies evaluating long-term pulmonary function. Large studies evaluating long-term pulmonary function after lung injury in critically ill children are more challenging because of the inability of young children to perform pulmonary function testing. In small studies evaluating pediatric patients surviving ARDS, survivors have varying risks of restrictive and obstructive

lung disease (Knoester et al. 2007; Ben-Abraham et al. 2002; Weiss et al. 1996). In a follow-up study evaluating 14 patients surviving ARDS with an average follow-up time of 23 months following discharge, 7/11 patients demonstrated evidence of restrictive or obstructive disease on spirometry (Weiss et al. 1996). In a study of seven children surviving ARDS, only one had mild exercise-induced hypoxemia (Ben-Abraham et al. 2002).

64.4 Affects of Mechanical Ventilation on Neuromuscular Function

Neuromuscular dysfunction is a common problem in critically ill patients and is a cause of major long-term morbidity in adults (Hermans et al. 2008). The incidence of neuromuscular dysfunction has been reported in 25–33 % of adult patients receiving mechanical ventilation for greater than 7 days and reaches 70–100 % in those with sepsis and multiorgan dysfunction (Hermans et al. 2008; Williams et al. 2007; Banwell et al. 2003; Hough et al. 2009). Critical illness myopathy (CIM) and critical illness polyneuropathy (CIP) are important causes of muscle weakness in critically ill patients and contribute to failure in weaning from mechanical ventilation (Hermans et al. 2008).

CIP and CIM belong to a spectrum of disorders causing muscle weakness in critically ill patients and can be difficult to differentiate clinically. Typically patients with CIP and CIM present with muscle weakness, muscle atrophy, and decreased or absent deep tendon reflexes. CIP is characteristic of axonal degeneration of motor and sensory fibers and can be differentiated from neuromuscular blockade (NMB) by normal repetitive nerve stimulation (Hermans et al. 2008). CIM is an acute myopathy that requires more specialized EMG testing, with muscle biopsy as the gold standard in differentiating CIM from CIP (Hermans et al. 2008). Both can be measured by nerve conduction studies and EMG. The Medical Research Council Sum Score (MRC) initially developed to evaluate patients with Guillain-Barre' syndrome is used to evaluate

CIP and CIM. The score measures muscle force on a scale from 0 to 5 in three muscle groups, with a maximum score of 60. Patients with a score <48 are diagnosed with CIP/CIM (Hermans et al. 2008).

Williams et al. (2007) reviewed the literature on CIP and CIM in the pediatric intensive care population in 2008 and found 34 cases of CIP/CIM in the literature. All 34 cases received mechanical ventilation, 20 were diagnosed with sepsis and or SIRS, five were diagnosed with asthma, and nine were recipients of solid organ or bone marrow transplantation. Twenty-one had received steroids and 24 had received neuromuscular blocking agents prior to the onset of weakness. Banwell et al. (2003) found a 1.7 % incidence of neuropathy following critical illness in 830 children without underlying neuromuscular disease. Of the 14 children with neuropathy, three patients died and four had repeated failure attempts at extubation. Of the children who underwent muscle biopsy, all showed evidence of acute quadriplegic myopathy. On 3-month follow-up, eight of the nine available survivors had persistent proximal muscle weakness of the upper and lower limbs. Two of those children were unable to walk independently (Banwell et al. 2003). This study identified neuropathy based on clinical exam, which has shown to be insensitive in the diagnosis of CIP and CIM in adults (Hermans et al. 2008) and may underestimate the true incidence of neuropathy following critical illness in children.

The role of corticosteroids and neuromuscular blockade in the development of neuromuscular dysfunction is controversial. CIM has been reported in patients treated with corticosteroids and neuromuscular blocking agents: however, this has not been evident in prospective studies. In a secondary analysis of the ARDS Network RCT of methylprednisolone versus placebo for persistent ARDS, Houghes et al. (2009) found evidence of neuromyopathy in 34 % of those studied, with no significant difference between the methylprednisolone and control groups. A diagnosis of neuromyopathy was significantly associated with prolonged mechanical ventilation.

64.5 Psychological and Functional Sequelae of Mechanical Ventilation

Critically ill children have been found to suffer from psychological sequelae following their pediatric intensive care stay. Psychological or emotional morbidity includes depression, anxiety, and post-traumatic stress disorder (PTSD). PTSD is a psychological condition that occurs following a traumatic or life-threatening event that triggers feelings of intense helplessness and fear. Patients exhibit symptoms of hyperarousal, intrusive recollections, and avoidance. PTSD and delusional memories have been associated with invasive procedures, duration of sedative use, severity of illness, and hospital length of stay (Rennick and Rashotte 2009; Rennick et al. 2002; Colville et al. 2008; Cichetti and Gamey 1993).

64.5.1 Post-traumatic Stress Disorder (PTSD)

PTSD has been associated with major impairments in the quality of life of adults surviving critical illness up to 8 years following recovery and has been linked to the number of adverse ICU related memories. Up to 30 % of PICU survivors have been found to have post-traumatic stress disorder (PTSD) while delusional memories have been reported to occur in nearly 33 % of children following their PICU stay (Rennick and Rashotte 2009; Rennick et al. 2002; Rees et al. 2004). In a review of 17 studies evaluating psychiatric disorders following critical illness, Davydow et al. (2010) reported PTSD and major depression as the most commonly assessed disorders. The point prevalence of PTSD ranged from 10 to 18 % and clinically significant depressive symptoms ranged from 7 to 13 %. Severity of illness and increased number of invasive procedures appeared to predict psychiatric illness in some but not all of the studies. Decreased emotional state has been reported in 22 % of children following a PICU stay (Gemke et al. 1995). Yet some children do well despite experiencing extreme stress (Cichetti

and Gamey 1993), and protective factors include temperament, family strength, presence of parents, and other external support (Davydow et al. 2010; Bender et al. 2000).

64.5.2 Functional Status Following Critical Illness

Measurement of functional health status in children can be challenging compared to that of adults. Independence is often a marker used to assess overall functional status in adults and is a reasonable goal to measure. However, in children, achieving independence is part of normal development and increases nonlinearly over time. Functional measures for children vary broadly by age complicating this measure, and prolonged intensive care unit stays occur during crucial points in a child's development. Furthermore, many of the measures developed address functional status following discharge and not functional status while hospitalized. Cognitive testing may be more relevant for the school-age child while motor and cognitive developmental markers are more useful in assessing the functional status of an infant or toddler.

Pollack et al. (2009), in 2010, developed a new scale to measure pediatric outcomes in hospitalized pediatric patients called the Functional Status Score (FSS) based on the model for measuring activities of daily living in adults and adapted for children where these activities change depending on the developmental stage of the child. The FSS was measured and validated in PICU, high-risk non-PICU, and technology-dependent children and correlated well with the ABASII: Adaptive Behavior Assessment System. The domains of functioning in the FSS include mental status, sensory functioning, communication, motor functioning, feeding, and respiratory status. Each domain was categorized as normal (score 1) to very severe dysfunction (score 5) and the total score ranged from 5 to 30. The measures of activities for daily living were adjusted for developmental stages, using adaptive behavior measures. The scale is a rapid and reliable way to measure the functional status in a pediatric

patient and well suited to measure outcomes in for the ICU population.

Cognitive impairments are common following critical illness in adults, with one study reporting cognitive impairment in 100 % of patients surviving ARDS. Cognitive testing in children is more difficult and must be modified for the child's stage of development. The Pediatric Cerebral Performance Category scale (PCPC) and the Pediatric Overall Performance Category scale (POPC) are both outcome measures used to measure short-term cognitive impairment and health status of pediatric ICU survivors. Both scales were developed by Fiser (1992) and are based on the Glasgow Outcome Scale modified for children. The PCPC scale ranges from 1 to 6, with 1 being normal at the age-appropriate level, i.e., a school-age child regularly attending school, and 6 being brain death. The POPC scale focuses more on physical function 1 being good overall performance, healthy, and capable of activities of daily life and 6 being brain death.

The Denver Developmental Screening Test (Frankenburg and Dodds 1967) and Bayley Mental and Motor Scales (Hack et al. 2000; Harris and Langkamp 1994) tests are widely used to assess the developmental status of infants and children. The Denver Developmental Screening

Test evaluates four domains, gross motor, language, fine motor-adaptive, and personal-social, while the Bayley Mental and Motor Scales are used to measure functional outcomes in infant. The Wee-Functional Independence Measure (Wee-FIM) (Msall et al. 1994) is a generic tool used to measure disability and burden across multiple domains and was adapted from the adult FIM scale (Keith et al. 1987). Often used in the rehabilitation setting, it has been used to measure victims following pediatric trauma. Table 64.2 summarizes the score used to measure functional status in children following critical illness.

Typpo et al. in 2010, performed a study of 44,693 admissions to 28 hospitals to determine chronic illness outcomes after admission with multiple organ dysfunction syndrome (MODS) for patients in the pediatric intensive care unit (PICU). Most children who survive critical illness return to baseline functional status; however, children with chronic illness had an increased incidence of MODS at admission to the MICU and increased mortality rates than previously healthy children. Children with MODS on day one of PICU admission had higher mortality rates, longer PICU length of stay, and larger changes in PCPC and POPC scores at discharge than those without MODS at day 1.

Table 64.2 Comparison of Functional Status Scores in children

	POPC/PCPC	FSS	DDST	VABS	Wee-FIM
Predicted outcome	Functional morbidity/cognitive impairment	Functional status/activities of daily living	Developmental status	Functional status	Functional status
Domains measured	Good overall performance	Sensory function	Gross motor	Communication	Independent self-care
	Mild overall disability	Communication	Language	Activities of daily living	Sphincter control
	Severe overall disability	Motor functioning	Fine motor-adaptive	Socialization	Transfers
	Coma or vegetative state	Feeding	Personal-social	Motor skills	Mobility
	Brain death	Respiratory status			Locomotion Communication Social cognition

PCPC Pediatric Cerebral Performance Category scale, *POPC* Pediatric Overall Performance Category scale, *FSS* Functional Status Scale, *Wee-FIM* Functional Independence Measure for Children, *DDST* Denver Developmental Screening Test, *VABS* Vineland Adaptive Behavior Scale

Fortunately, the majority of children surviving critical illness will return to their baseline functional status.

64.6 Quality of Life After Mechanical Ventilation

A child’s overall quality of life often is impacted by critical illness and mechanical ventilation. In adults, Health-Related Quality of Life is measured using the Short Form 36 (SF-36) and has been used in pediatric burn survivors (Butt et al. 1990). Quality of life following recovery from critical illness and discharge from the pediatric intensive care unit has been studied in children using tools adapted to measure Health-Related Quality of Life in children (HRQL) (Butt et al. 1990; Morrison et al. 2002; Sheridan et al. 2000). The Health-Related Quality of Life in children incorporates functional status, an individual’s perceptions of well-being, and satisfaction with life. Measures of quality of life in infants and younger children are more difficult to evaluate. In this age group, HRQL measures are dependent on parental report and can be influenced by parental health (Waters et al. 2000).

The Health Utilities Index is another tool used to measure HRQL in children and incorporates health status measures and quality of life measures, using the MARK I, II, and III scales.

In 2009, Conlon et al. (2009) evaluated the quality of life in pediatric patients requiring ≥ 28 days of ICU care using the Pediatric Quality of Life inventory (Peds QL 4.0). Of the 125 survivors given the questionnaire, 70 responded. Fifty-seven percent of survivors reported a normal quality of life and 42.9 % reported an impaired HRQL. Of those reporting impaired quality of life, 20 % had ongoing disabling health problems (Conlon et al. 2009). These findings are similar to other studies, where 50–70 % of PICU survivors return to the same quality of life as before admission and 60 % return to normal functional health (Knoester et al. 2007).

Using a single global functioning scale, Morrison et al. (2002) studied 434 pediatric ICU (PICU) survivors and found fair or poor quality of life in 34 % of the children. In a study of 303 previously healthy children, Butt et al. (1990) found that 14 % of patients had reported impairment up to 3 years following discharge. Other studies have measured functional status longitudinally and have found impairment from baseline in more than a third of previously healthy pediatric ICU survivors (Fiser 1992; Typo et al. 2010; Taylor et al. 2003). Further studies are needed to evaluate the impact of critical illness and specifically mechanical ventilation on the quality of life on children surviving critical illness. Table 64.3 summarizes the tools used to measure quality of life in pediatric ICU survivors.

Table 64.3 Comparison of quality of life measure in children

	HUI Mark III	Peds QL 4.0	CHIP	SF-36
Predicted outcome	Quality of life	Quality of life	Quality of life in adolescents	Quality of life in adults
Domains measured	Vision	Physical function	Activity	Physical functioning
	Hearing	Emotional function	Comfort	Role limitations due to physical health
	Speech	Social function	Satisfaction	Bodily pain
	Ambulation	School function	Disorders	General health perceptions
	Dexterity		Achievement	Vitality
	Emotion		Resilience	Social functioning
	Cognition			Limitations due to emotional problems
	Pain			Mental health

HUS Health Utilities Index, *CHIP* adolescent child health and illness profile

64.7 Summary

Mortality rates in children surviving critical illness and mechanical ventilation continue to decrease, making the measure of outcomes following survival crucial. Mechanical ventilation is indispensable in our care of children with respiratory failure; however, it is crucial to understand the potential sequelae of mechanical ventilation on pulmonary and neuromuscular function as well as the impact critical illness has on functional status and quality of life. Critical illness impacts a patient's physical, developmental, psychological, and overall well-being, as well as quality of life.

Tools that measure these short- and long-term outcomes in survivors of critical illness and mechanical ventilation are important in our understanding of the impact of critical illness on our patients and families. Outcome scores to measure morbidity and mortality are often used in the pediatric ICU to estimate severity of illness, but however are not meant to predict long-term outcomes. Long-term outcomes are more difficult to measure and are equally important in our understanding of the long-term impact of critical illness and our subsequent treatments on patients and their families. Measuring long-term outcomes and functional status in children following critical illness is more challenging than in adult given the difficulty in measuring independence in an infant and small child. New measures, such as the Functional Status Score, are promising new tools to measure outcomes in the hospital and following discharge.

sured after hospital discharge and/or are permanent. Mortality is the most commonly measured ICU outcome and it influences both short- and long-term outcomes.

- Complications from intubation and mechanical ventilation, such as injury to the upper airway, ventilator-induced lung injury, and ventilator-associated pneumonia, can occur in infants and children and may lead to altered long-term pulmonary function.
- Neuromuscular dysfunction is a common problem in adults surviving critical illness and is a cause of major long-term morbidity. Neuromuscular dysfunction such as critical illness myopathy and neuromyopathy occur in critically ill children; however, the long-term morbidity is currently unknown.
- Measuring functional status in children following critical illness is crucial to understand the long-term effects of mechanical ventilation; however, it is challenging given that achieving independence is part of normal development and increases nonlinearly over time.
- Quantifying the psychological impact of critical illness, as well as the impact critical illness has on quality of life, is crucial in understanding the long-term outcomes in PICU survivors.

Essentials to Remember

- As pediatric ICU care advances and mortality rates for critically ill children continue to decline, it is increasingly important to consider the short- and long-term outcomes of patients surviving critical illness.
- Short-term outcome measures are those evaluated during the pediatric ICU stay and/or hospital stay. Longer-term outcome measures are those that are mea-

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Part XXV

Mechanical Ventilation in the Operating Room

Joseph D. Tobias

During the provision of general anesthesia, some type of support of ventilatory function is generally necessary given the depressant effects of the various anesthetic and opioid agents that are administered to provide amnesia and analgesia. Furthermore, for major thoracic or abdominal procedures, neuromuscular blocking agents are frequently administered, thereby necessitating full control of ventilation. As with ventilation outside of the operating room (OR), variation options exist for respiratory support during the provision of general anesthesia including volume- or pressure-limited modalities or more recently the use of pressure support ventilation to augment spontaneous ventilation. Given the limitations of commercially available OR ventilators, critically ill patients may require the use of sophisticated ICU ventilators in the OR setting. In such instances, as the inhalational anesthetic agents cannot generally and easily be administered through such ventilators, general anesthesia

is provided by intravenous anesthetic agents (total intravenous anesthesia or TIVA). This chapter reviews the basics of anesthesia breathing systems, options for ventilator support during anesthetic care, and special situations in the operating including the administration of adjunctive agents (helium, nitric oxide, nitrogen, and carbon dioxide) as well as the use of one-lung ventilation (OLV) during thoracic surgical procedures.

65.1 Breathing Systems in the Operating Room

The general design of the anesthesia machine consists of a gas source for oxygen, air and nitrous oxide, flow meters, vaporizers, and a common gas outlet. The gas source is generally from a hospital-based system with wall outlets, although in remote areas of the hospital or in inauspicious surroundings, the source of gases can be standard tanks. The gases (oxygen, air, and nitrous oxide) are mixed using flow meters and then directed into the vaporizers for the delivery of various concentrations of the inhalational anesthetic agents. The inhalational anesthetic agents (sevoflurane, desflurane, and isoflurane) are volatile liquids, meaning that they have the potential to transform into a vapor. As the concentration on the vaporizer dial is increased, more of the gas flow is diverted through the vaporizer, thereby increasing the inspired concentration of the inhalational anesthetic agent. In today's clinical practice, there is a

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specific vaporizer calibrated for each of the various inhalational anesthetic agents as the vapor pressure varies from agent to agent. As the gas flow exits the vaporizer, it is directed toward the patient through the common gas outlet.

65.1.1 Open, Semi-open, Semi-closed, and Closed Breathing Systems

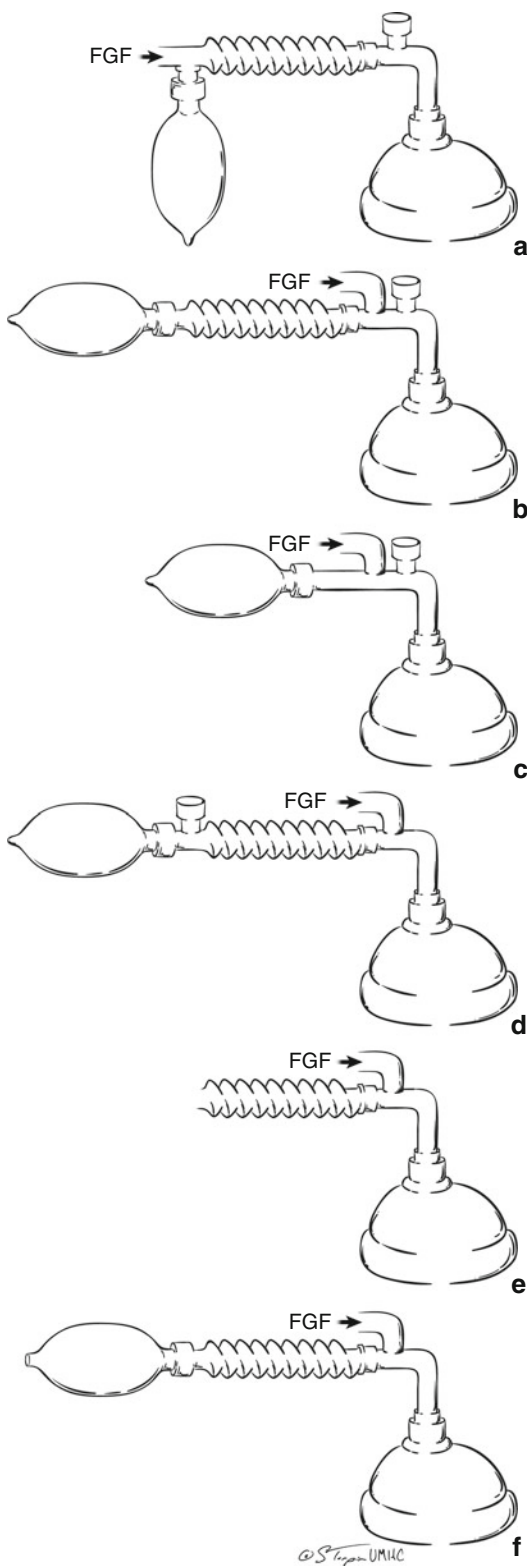
As the gas exits the anesthesia machine, it is delivered to the patient through the anesthesia circuit. The function of the circuit involves both the delivery and the removal of the exhaled gas from the patient. As the exhaled gas contains carbon dioxide, some means of its removal is mandatory to avoid rebreathing and the development of significant hypercarbia. This can be accomplished either by a high fresh gas flow (FGF) or the inclusion of a substance into the anesthesia system that will absorb the carbon dioxide (see below). The rebreathing of exhaled gases during general anesthesia is in marked distinction to what occurs in the ICU setting where the entire exhaled tidal breath is vented away from the patient, and therefore, no rebreathing occurs. Advantages of partial or complete rebreathing include conservation of gases (oxygen, air), heat, airway humidity, and inhalational anesthetic agents. Additionally, the semi-closed or closed systems reduce environmental pollution.

In general, anesthetic delivery systems are classified as open, semi-open, semi-closed, and closed. In current practice, open systems, which are exemplified by the administration of open-drop ether using a specialized mask wire frame mask developed by Dr. Schimmelbusch, are no longer in use. Although the semi-open, semi-closed, and closed designation is still in common use, a more appropriate terminology may be to divide systems into those where there is no rebreathing of exhaled gases (open and semi-open) and those in which there is rebreathing of exhaled gases (semi-closed and closed) (Conway 1985; Miller 1988). In systems with some or complete rebreathing, a CO₂ absorber is added in-line to remove CO₂ from the exhaled gases.

65.1.1.1 The Mapleson Breathing Systems

The era of modern-day anesthesia circuits was brought to anesthesia practice by the description and introduction into practice of the Mapleson systems (Mapleson 1954). The Mapleson systems includes five different configurations of the FGF, tubing, reservoir bag, and expiratory valve (Fig. 65.1). When compared with a standard circle system (see below), the Mapleson system does not have an inspiratory valve and was developed as such to limit the work of breathing in younger infants. The amount of rebreathing of exhaled gases that occurs with each system depends significantly on the patient's minute ventilation and the FGF rate. Modifications of the original Mapleson system include the addition of a sixth setup (the F system) and the Bain circuit. The F system is a modification of the E system (Ayre's t-piece) where a reservoir bag is placed at the end of the corrugated tubing (Willis et al. 1975). The reservoir bag is open at the distal end (away from the corrugated tubing) and can be occluded between the anesthesiologist's fingers or a clamp to allow for assisted or positive-pressure ventilation. When used in this fashion, it is commonly known as the Jackson-Rees modification of the Ayre's t-piece. An additional modification of the F system or Jackson-Rees modification of the Ayre's t-piece known as the Kuhn's circuit has a hole in the side of the reservoir bag instead of the end.

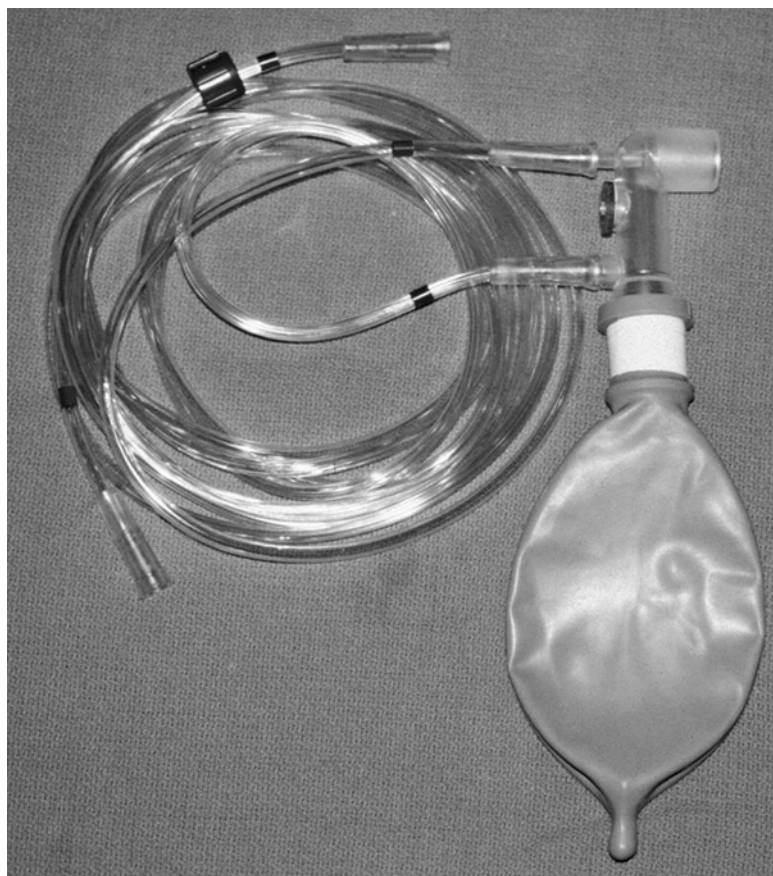
The Mapleson A circuit, also known as the Magill's circuit, has the FGF coming into a corrugated tube, a reservoir bag at the end of the corrugated tubing, and a one-way expiratory valve at the end of the corrugated tubing just proximal to the attachment to the patient (ETT, mask, or laryngeal mask airway). This arrangement is most efficient during spontaneous ventilation as rebreathing does not occur until the FGF is below 70 % of the patient's minute ventilation (Norman et al. 1967; Kain and Nunn 1967). However, the system is inefficient during positive-pressure ventilation as the expiratory valve must be closed to such a degree that there is limited venting of exhaled gases, thereby



resulting in rebreathing. As such, the device is not recommended for use during controlled ventilation (Kain and Nunn 1968; Sykes 1959). The Mapleson B differs from the Mapleson A in that the FGF is adjacent to the expiratory valve at the end of the corrugated tubing. Given the placement of the FGF, the system's efficiency is similar during spontaneous and controlled ventilation. The position of the FGF allows fresh gas and exhaled gases to accumulate in the corrugated tubing until the pressure increases to such a point that the gas is expelled through the expiratory valve. The gas that is expelled is a mixture of fresh gas and exhaled alveolar gas with the exact percentage of the two depending on the FGF rate. Rebreathing does not occur when the FGF rate is more than twice the minute ventilation during either controlled or spontaneous ventilation (Sykes 1968). The Mapleson C system, also known as the Waters' circuit without a CO₂ absorber, has a setup and design similar to that of the Mapleson B with a much shorter piece of tubing from the bag to elbow adaptor for attachment to the patient. As with the Mapleson B, the pop-off valve is located on the elbow adaptor. The elimination of the tubing or use of a shorter piece of tubing results in greater mixing of exhaled and inspired gases. An FGF of twice the minute ventilation is required to prevent rebreathing of exhaled CO₂. A similar device (Fig. 65.2) has been adapted for use during neonatal and pediatric resuscitation to provide pre-oxygenation and ventilation prior to endotracheal intubation. The modification of the Mapleson C device for resuscitation includes not only an inlet for the delivery of FGF, which is usually connected to a high-pressure oxygen source (wall outlet or standard E cylinder), but also a second attachment site which is hooked to a

Fig. 65.1 Arrangement of the various Mapleson circuits (a–f). The circuits vary based on the site of introduction of the fresh gas flow (FGF), pop-off or airway pressure relief valve, reservoir bag, and corrugated tubing. The arrangements vary significantly in their efficiency in carbon dioxide removal during either controlled or spontaneous ventilation

Fig. 65.2 Photograph of a Mapleson C circuit setup which is commonly used during resuscitation for positive-pressure or spontaneous ventilation through an anesthesia mask or an endotracheal tube. The tubing is connected to an oxygen source and a manometer. The adjustable pop-off valve lies between the two connection sites for the tubing



manometer to allow for pressure measurements during positive-pressure ventilation or the delivery of CPAP. When compared to a standard resuscitation bag (Ambu bag), advantages of the Mapleson C design include the ability to provide an FiO_2 of 1.0 for resuscitation, preoxygenation, transport, or positive-pressure ventilation; the ability to accurately assess and change the level of positive-pressure ventilation with the use of a manometer; the ability to deliver CPAP during spontaneous ventilation; and the ability to spontaneously ventilate with limited airway resistance. Additionally, when the modified Mapleson C is attached to an oxygen blender, the FiO_2 can be effectively and accurately adjusted for situations where positive-pressure ventilation with a varying FiO_2 may be indicated such as infants with single-ventricle physiology or during neonatal resuscitation. The Mapleson D system differs from the Mapleson B only in the location of

the pop-off valve. With the Mapleson D, the pop-off valve is located near the reservoir bag instead of on the elbow adaptor. During exhalation, the exhaled gas travels down the corrugated tubing and mixes with the FGF. The composition of the inspired gas is therefore determined by the FGF rate, the exhaled tidal volume, and the expiratory time. A long expiratory time as will occur with a slow respiratory rate results in a longer time for the exhaled gas to flow down the corrugated tubing and be washed out of the circuit through the expiratory valve by the FGF. The system is most efficient during controlled ventilation with a requirement for an FGF rate less than that of the Mapleson A, B, or C system. During spontaneous ventilation, the FGF rate should be approximately twice the minute ventilation to prevent rebreathing (Bain and Spoerel 1973; Soliman and Laberge 1978). A modification of the Mapleson D circuit, known as the

Bain system, functions in a manner equivalent to that of the Mapleson D. The difference with the Bain system is that the FGF travels inside the corrugated tubing, therefore allowing the exhaled gas to warm the FGF prior to its administration to the patient. However, the disadvantage of the system is that the FGF line cannot be visualized in the event of its occlusion, disconnection, or kinking.

The Mapleson E and F systems are similar and differ only in the addition of a reservoir bag at the end of the corrugated tubing in the Mapleson F system. As opposed to the other Mapleson systems, neither of these systems has a pop-off valve incorporated into the elbow adaptor or the tubing system. The Mapleson E system was a modification of the Ayre's t-piece which was developed in the 1930s by Dr. Phillip Ayre for use during pediatric anesthesia (Ayre 1937). The Mapleson E system or some modification of its design is commonly used to administer oxygen during spontaneous ventilation through an ETT. It has no valves, thereby limiting resistance to breathing and hence the work of breathing and minimal dead space, and it permits the elimination of rebreathing with FGF rates of two to three times the minute ventilation. The reservoir space of the tubing prevents entrainment of room air provided that the tidal volume is less than the dead space of the tubing. As there is no reservoir bag on the Mapleson E, it cannot be used for positive-pressure ventilation. The modification of the Mapleson E by the addition of the reservoir B at the end of the corrugated tubing results in the Mapleson F system (more commonly known as the Jackson-Rees modification of the Ayre's t-piece). For use during positive-pressure ventilation, a pop-off valve is incorporated into the reservoir bag. This opening in the bag can be occluded by the anesthesia provider to provide CPAP during spontaneous ventilation to allow for positive-pressure ventilation. Based on the FGF rate and the occlusion of the hole, the CPAP or peak inspiratory pressure can be altered. With the Mapleson F system (Jackson-Rees modification of the Ayre's t-piece), the hole is at the distal end of the reservoir bag and can be occluded between two fingers of the anesthesia provider or

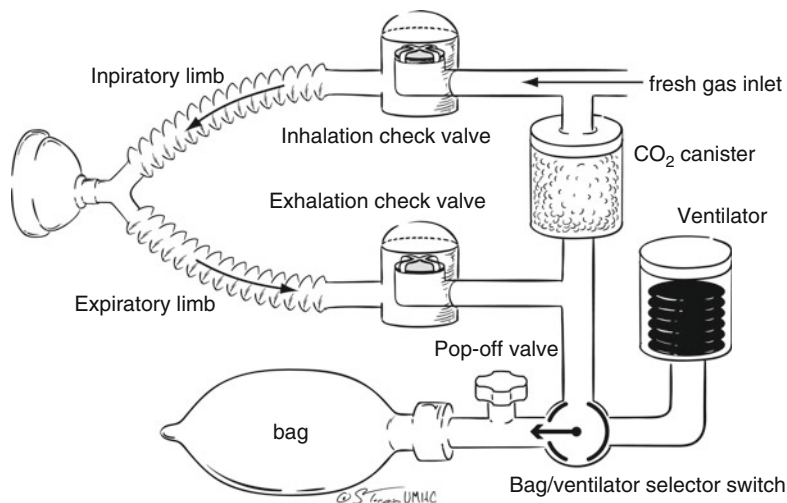
with a t-clamp. Alternatively, the hole in the reservoir bag can be on its side (Kuhn's circuit). FGF rates are similar to those described for the Mapleson D circuit.

Advantages of the Mapleson circuits which maintains their use in the practice of pediatric anesthesia include the ability to switch from controlled to spontaneous ventilation; limited inspiratory resistance and absence of valves, thereby decreasing work of breathing during spontaneous ventilation; and a long history of their use in the provision of pediatric anesthesia. Disadvantages include requirements for high FGF rates with the use of larger quantities of air/oxygen/nitrous oxide; no rebreathing, thereby increasing the requirements and cost of inhalational anesthesia; no humidification or heating of the inspired gas (this can be overcome by the inclusion of a heated humidifier to warm and humidify the FGF prior to its entry into the Mapleson system); and increased environmental pollution.

65.1.1.2 The Circle Anesthesia Breathing Systems

Given these concerns, there is increasing use of a standard circle system (Fig. 65.3) for the provision of anesthesia in the USA. The circle systems are semi-closed systems as rebreathing of the exhaled gases occurs depending on the FGF rate. As such, to prevent issues with the rebreathing of CO₂, some type of CO₂ absorber is required in these systems. Unidirectional valves direct the FGF toward the patient and the expiratory gases toward the CO₂ absorber or the exhalation valve, thereby limiting rebreathing when the FGF is decreased. With these systems, although the extent of rebreathing is determined primarily by the FGF, very low FGF rates (less than 500 mL/min in an adult) can be used since the CO₂ is eliminated from the exhaled gases and rebreathing serves to conserve heat, humidity, and anesthetic gases. The circle system serves to define and distinguish between the different types of anesthesia breathing systems as it can be used as a semi-open (no rebreathing), semi-closed (partial rebreathing), or closed (complete rebreathing) system based on the FGF rate (Moyers 1953). The circle system consists of several key

Fig. 65.3 Arrangement of the standard anesthesia circle system used in modern operating rooms for the delivery of anesthetic agents and gas mixtures (oxygen, air, and nitrogen)



elements including an FGF source, inspiratory and expiratory valves, inspiratory and expiratory corrugated tubing, a Y piece which connects with the standard 15 mm on the airway device (ETT, anesthesia mask, or laryngeal mask airway), a pop-off valve otherwise known as the airway pressure relief (APR) valve, a reservoir bag, and the CO₂ absorber cannister. The diameter of the corrugated tubing comes in various sizes to limit the dead space for pediatric patients. Additionally, specialized tubing is available which allows adjustment of the length of the inspiratory and expiratory limbs of the system to allow for the provision of general anesthesia in situations where the anesthesia machine must be placed some distance from the patient due to the presence of other personnel or apparatus such as the cardiac catheterization suite, radiology suite, or during magnetic resonance imaging. However, when the tubing is expanded, the dead space may increase, necessitating the increase of the FGF rate to prevent rebreathing from the dead space of the tubing. During the provision of anesthesia, the amount or presence of rebreathing can easily be assessed by using the end-tidal CO₂ monitor which provides not only expiratory CO₂ values (end tidal) but also inspiratory values which should be zero if there is adequate gas flow to wash out the CO₂ from the dead space of the circuit.

65.1.1.3 Carbon Dioxide Absorbers

As some rebreathing of exhaled gases generally occurs with the use of a circle system, a mechanism for scrubbing or removing the exhaled CO₂ must be in place. It has minimal dead space and no valves, thereby limiting resistance to breathing and hence the work of breathing. Additionally, it eliminates rebreathing with FGF rates of two to three times minute ventilation. In most circumstances, the rebreathing of exhaled gas is beneficial as it serves to conserve heat and humidity as the exhaled gases are already warmed and humidified as well as decreasing the cost of the care by limiting the need for the inhalational anesthetic agent. The latter is quite important as rebreathing of the exhaled gas and therefore the exhaled inhalational anesthetic agent allows for the decrease in the FGF rate to less than 1 L/min in some cases, thereby significantly decreasing the consumption of the inhalational anesthetic agent. However, whenever exhaled gases are rebreathed, hypercarbia will occur unless the carbon dioxide is removed or “scrubbed” from the exhaled gas. In clinical anesthesia, this is accomplished by passing the exhaled gas over a substance which removes the exhaled carbon dioxide. A similar process is used in other closed areas such as submarines to prevent the rebreathing of exhaled carbon dioxide.

In clinical anesthesia practice, one of three similar substances is used to remove the carbon dioxide from the exhaled gas: soda lime, baralyme, or calcium hydroxide lime (Amsorb). Soda lime, a mixture of chemicals in granular form, removes the carbon dioxide from the exhaled gases. Soda lime is produced by treating slaked lime with a concentrated sodium hydroxide solution. The main components of soda lime are calcium hydroxide or $\text{Ca}(\text{OH})_2$ (75–70 %), water (15–20 %), sodium hydroxide or NaOH (3–4 %), and potassium hydroxide or KOH (1 %). The exothermic chemical reaction for the removal of carbon dioxide by soda lime can be summarized as $\text{CO}_2 + \text{Ca}(\text{OH})_2 \rightarrow \text{CaCO}_3 + \text{H}_2\text{O} + \text{heat}$. Baralyme is a mixture of approximately 80 % calcium hydroxide and 20 % barium hydroxide. Calcium hydroxide lime (Amsorb) is the newest of the three agents available for carbon dioxide scrubbing. The impetus for the production of this agent was to provide an effective agent for carbon dioxide removal that does not contain either sodium or potassium hydroxides. The advantage of the elimination of these agents is that the new product (Amsorb) does not interact with the inhalational anesthetic agents to produce toxic by-products such as carbon monoxide or compound A (see below) (Versichelen et al. 2001).

The production of the carbon dioxide absorbers as a granular form has been studied by trial and error to produce granules which maximize the surface area for the absorption of carbon dioxide and minimize the resistance of the gas as it flows over these granules in the cannister (Hunt 1955). The granule size of soda lime and baralyme is measured in units known as mesh which refers to the number of openings per linear inch in a sieve through which the granules can pass. Soda lime and baralyme have granules that vary in size from 4 to 8 mesh which results in an adequate absorptive surface area for the removal of carbon dioxide with a minimal increase in the resistance to gas flow. In addition to the compounds which absorb carbon dioxide, an indicator is added to these agents to provide a warning that the agent is becoming exhausted or is no

longer capable of removing carbon dioxide. As the carbon dioxide absorbing capacity becomes depleted, the pH of the granules decreases and the indicator (ethyl violet) turns from colorless to purple.

Although effective for the removal of carbon dioxide, recent evidence has suggested that the interaction of the carbon dioxide absorbent and various inhalational anesthetic agents may result in potentially deleterious effects including either the production of a toxic compound (compound A or carbon monoxide) or the production of excessive heat with the risk of thermal injury to the airway or production of a fire in the cannister (Fang et al. 1995; Baum et al. 1995). Only carbon dioxide absorbents that contain KOH or NaOH (soda lime and baralyme) can result in the production of carbon monoxide or compound A. No such interaction exists with the newer agent, Amsorb.

The potential interaction of inhalational anesthetic agents and the carbon dioxide absorbent is nothing new in the practice of clinical anesthesia. Such issues were first recognized in the 1950 and 1960s with the inhalational anesthetic agent, trichloroethylene which produces a neurotoxin, dichloroacetylene, and a respiratory toxin or irritant, phosgene. Such problems still potentially exist even with the use of the modern inhalational anesthetic agents. The vinyl ether, compound A, is produced during the metabolism of sevoflurane and its reaction with the soda lime or baralyme in the carbon dioxide absorber of the anesthesia machine (Morio et al. 1992; Frink et al. 1992). The safe concentration of compound A is unknown in humans as is the mechanism of the postulated renal injury (Mazze 1992). Compound A concentrations are increased by several factors including a high inspired concentration of sevoflurane, a low FGF through the system (less than 2 L/min), increasing temperatures of the soda lime cannister, the water content of the CO_2 absorbent, and high concentrations of potassium or sodium hydroxides in the CO_2 absorbent. Despite the demonstration of potentially nephrotoxic effects of compound A in laboratory animals, even in patients with preexisting renal

dysfunction, there are no data to suggest that sevoflurane and compound A lead result in clinical consequences on renal function even during prolonged anesthetics.

Another issue of potential concern regarding the interaction of the inhalational anesthetic agents and the carbon dioxide absorbents is the production of carbon monoxide. Clinically significant amounts of carbon monoxide are produced only when desiccated soda lime or baralyme is used in conjunction with desflurane or the older inhalational anesthetic agent, enflurane (Fang et al. 1995; Baum et al. 1995). The scenario of carbon monoxide toxicity related to such issues has most commonly reported with the first case on a Monday morning when the fresh gas has been left flowing through the anesthesia machine over the weekend resulting in the desiccation of the carbon dioxide absorbent (Berry et al. 1999). Although an extremely rare event, significant morbidity and mortality may occur as carboxyhemoglobin levels of up to 30 % have been reported (Berry et al. 1999). Factors which may increase the production of carbon monoxide include the inhalational anesthetic agent used (desflurane, enflurane) and its inspired concentration, the type of carbon dioxide absorbent, and the water content and temperature of the absorbent.

One final consequence of the use of carbon dioxide absorbents is the potential for an accelerated exothermic reaction with the subsequent generation of significant amounts of heat which, in rare circumstances, can result in the production of a fire. In 2004, Abbott laboratories released a dear healthcare provider letter, and warnings were published in the Anesthesia Patient Safety Foundation letter regarding the potential for an exothermic reaction leading to fires from the interaction of sevoflurane and the CO₂ absorbent, Baralyme®. To date, this has been an extremely rare occurrence with a limited number of reports in the literature (Castro et al. 2004; Wu et al. 2004; Fatheree and Leighton 2004). As was noted with the issues regarding the release of carbon monoxide from the interaction of the CO₂ absorbent and the inhalational anesthetic agents (see above), the exothermic reaction from the

interaction of sevoflurane and Baralyme® occurs only under extreme circumstances when the CO₂ absorbent has been desiccated from prolonged high gas flows. Therefore, with proper care and attention, such issues should not be a concern during the routine provision of general anesthesia. However, the potential impact and danger of the extreme circumstances (desiccated CO₂ absorbent, high fresh gas flow, and high sevoflurane concentration) are demonstrated by the study of Laster et al. using a lung analogue model (Laster et al. 2004). Baralyme® was desiccated by a heated high oxygen flow for several hours. The CO₂ absorbent was then placed in a standard cannister on an anesthesia machine and a 6 L/min flow of oxygen directed through it with either 1.5 MAC of sevoflurane or both 1.5 and 3 MAC of desflurane and isoflurane. A 3-L resuscitation bag was used as a lung model and a minute ventilation of 10 L/min started. With either 1.5 or 3 MAC of isoflurane and desflurane, the temperature within the cannister increased to a peak of approximately 100 °C after 30–70 min. With 1.5 MAC of sevoflurane, the temperature increased to more than 200 °C, and in two of the five cases, flames were noted in the anesthesia circuit.

65.2 Intraoperative Mechanical Ventilation

There are several obvious differences between mechanical ventilation in the operating room and that performed in the ICU setting. In the operating room setting, airway control may be provided by an anesthesia mask, a supraglottic airway device such as the laryngeal mask airway, or an endotracheal tube. As opposed to the ICU setting, the operating room is unusual in that many patients who receive mechanical ventilation have relatively normal pulmonary function and receive endotracheal intubation and controlled ventilation only because of the requirements for the surgical procedure. However, other extremes exist in that patients may have preexisting pulmonary comorbidities which require meticulous intraoperative attention to

their requirements for mechanical ventilation. Alternatively, significant intraoperative or postoperative issues may develop (bronchospasm, acid aspiration, laryngospasm) which may require impact on respiratory function.

65.2.1 Controlled Ventilation

Although generally not as efficient as ICU ventilators, the newest generation of anesthesia ventilators allows various options for the mode of ventilation including pressure- or volume-limited ventilation as well as pressure support ventilation during spontaneous ventilation. As in the pediatric ICU, the goals of mechanical ventilation are to provide ventilation (removal of CO₂) and oxygenation. In many circumstances, anesthesia ventilators work in the IMV (intermittent mandatory ventilation) mode so that there is no synchronization with spontaneous ventilation. In fact, when potent inhalational anesthetic agents, high doses of propofol, or high doses of opioids are administered, they shift the CO₂ response curve to the right to such an extent that the patient's ventilatory drive is abolished. Additionally, for specific types of surgical procedures (thoracic or neurosurgery) when spontaneous ventilation may be undesirable or deleterious, neuromuscular blocking agents are added to the anesthetic regimen. Given these scenarios, CMV is used most commonly during the intraoperative period. As in the pediatric ICU, ventilation in the operating room is named by the limit variable (pressure or volume) or the parameter which is set to determine the magnitude of the tidal breath. In adult anesthesia practice, the limit variable is most frequently volume. A preset tidal volume is chosen (generally 6–8 mL/kg) and delivered at a rate per minute based on one's assessment of the patient's needs for minute ventilation. Alternatively, a pressure limit is used, and the tidal breath provided until a present pressure limit is achieved (pressure-limited ventilation). In general clinical practice, there are no data to demonstrate advantages of one mode over another; however, in specific clinical scenarios, there may be advantages to pressure-limited ventilation. Unzueta et al.

randomized 58 adult patients with good preoperative pulmonary function scheduled for thoracic surgery requiring one-lung ventilation (OLV) into two groups (Unzueta et al. 2007). Patients received a tidal volume of 9 mL/kg delivered either by volume-limited ventilation for 30 min followed by pressure-limited ventilation for a similar period of time or by pressure-limited ventilation for 30 min followed by volume-limited ventilation for a similar duration. Although they noted no difference in the oxygenation during the two modes of ventilation, the peak airway pressure required to deliver the tidal volume of 9 mL/kg was lower with pressure-limited ventilation (24.43 ± 3.42 versus 34.16 ± 5.21 cmH₂O, $p < 0.001$).

In addition to choosing the mode of ventilation, the pressure or volume limit, and the rate, anesthesia ventilators allow the setting of an inspiratory time. Although an often forgotten parameter, the inspiratory time can impact on both CO₂ removal and oxygenation via its effects on tidal volume and mean airway pressure. With volume-limited ventilation, a specific tidal volume is set and an inspiratory time is chosen. The flow provided is then integrated based on the tidal volume and inspiratory time. For example, if a V_T of 500 mL with an inspiratory time of 1 s is chosen, 500 mL will be delivered over 1 s using a gas flow of 30 L/min (500 mL/1 s = 60 L/min). Therefore, during volume-limited ventilation, increasing the inspiratory time will result in a decrease in the flow rate and the delivery of that tidal volume with a lower peak inflating pressure. As such, lengthening of the inspiratory time during the provision of general anesthesia is most frequently performed in patients with altered resistance and compliance as a means of delivering the tidal volume with a lower peak inflating pressure. As most pressure ventilators actually time cycle (end inspiration based on the inspiratory time), increasing the inspiratory time will increase the mean airway pressure and hence the exhaled tidal volume. The increased mean airway pressure improves oxygenation, while the increased tidal volume increases minute ventilation.

With normal spontaneous ventilation, the I:E ratio is 1:3 or 1:4. Therefore, the use of longer

inspiratory times may be uncomfortable during spontaneous ventilation, generally not an issue in the operating room during the provision of general anesthesia. In our practice, we frequently use inspiratory times of 0.3–0.5 s for infants and up to 0.7–1.5 s in adolescents. The inspiratory time should also be adjusted based on the underlying disease process. Patients with bronchospasm and air trapping generally benefit from a shorter inspiratory time to allow for as much exhalation time as possible. Patients with alveolar space disease and poor compliance generally do better with longer inspiratory times to increase mean airway pressure and improve oxygenation. The inspiratory time can be increased up to 1.2–1.5 s as needed to increase mean airway pressure and recruit alveoli, but our practice generally restricts the inspiratory time to limit the *I:E* at 1:1. Reversal of the *I:E* ratio has been used in the management of patients with severe ARDS in attempts to augment oxygenation and allow weaning of the FiO_2 (Schuster et al. 1991). However, longer inspiratory times especially when combined with higher ventilator rates can result in reversal of the *I:E* ratio which may result in inadequate exhalation times. This may result in air trapping, the stacking of one breath on another (inspiration for the next breath starting before exhalation), thereby resulting auto-PEEP.

Various mechanisms are available for adjusting the inspiratory time, which vary depending on the make and model of the anesthesia ventilator. The inspiratory time may be set as a fixed time (seconds), by adjusting the inspiratory flow rate, as an *I:E* ratio or as a percentage of the respiratory cycle. If the inspiratory time is set as an *I:E* ratio or as a percentage of the respiratory cycle, adjusting the rate will affect the actual inspiratory time. For example, if the respiratory rate is set at 15 breaths/min with an inspiratory time of 25 % or an *I:E* ratio of 1:3, this results in an inspiratory time of 1 s. Changing the rate to 20 breaths/min with the same inspiratory time of 25 % or *I:E* ratio of 1:3 now results in an inspiratory time of 0.75 s. Such changes can result in changes in the peak airway pressure during volume-limited ventilation or tidal volume during pressure-limited ventilation.

Another option on many anesthesia ventilators is the addition of an inspiratory pause. This time is added to the end of inspiration, thereby lengthening the inspiratory time, so its contribution to the total inspiratory time must be realized to avoid inadvertent reversal of the *I:E* ratio. This maneuver serves many of the same purposes as lengthening the inspiratory time including the recruitment of alveoli with long time constants (high resistance and low compliance), promotion of collateral ventilation via pores of Cohn and canals of Lambert, reversal of atelectasis, and improved matching of ventilation and perfusion. The inspiratory pause increases mean airway pressure, thereby improving oxygenation. Its effects on compliance result from the resolution of atelectasis and recruitment of lung units.

When considering mechanical ventilation in the operating room, the IMV mode is generally used based on the lack of spontaneous ventilation during many types of general anesthesia and the functioning parameters of operating room ventilators. However, other parameters are set very much in the same manner as they are in the pediatric ICU. The decisions to be made include (a) the limit variable (pressure or volume) which will control the tidal breath and its magnitude, (b) the inspiratory time, (c) the ventilator rate (breaths/min), (e) the FiO_2 , and (f) the PEEP. The rate is set primarily based on the patient's age, the desired PaCO_2 level, and the V_T that is delivered. In patients with severe lung injury, poor resistance, or altered compliance, higher rates are used to compensate for lower tidal volumes, thereby limiting ventilator-induced lung injury. Guidelines for starting ranges of respiratory rates include 10–12 breaths/min for an adolescent, 12–16 breaths/min for an older child (6–10 years of age), 16–24 breaths/min for a toddler, and 24–30 breaths/min for a neonate. Higher rates may be needed in patients with more severe degrees of lung injury, when hyperventilation is used to treat increased intracranial pressure or pulmonary hypertension, or if endogenous CO_2 production is elevated. The actual rate can be further adjusted based on the ETCO_2 which is routinely used for every general anesthetic as part of the guidelines for intraoperative monitoring.

Oxygenation is controlled by mean airway pressure and the inspired oxygen concentration (FiO_2). As many factors including general anesthetic agents and neuromuscular blocking agents may decrease functional residual capacity (FRC) especially in infants and children, the anesthetized patient may be prone to develop hypoxemia due to the development of atelectasis and the resultant ventilation–perfusion inequalities. The latter can be prevented by strategies that maintain an effective mean airway pressure including the peak inflating pressure, PEEP, and the inspiratory time. The actual contribution and setting for each can be adjusted much the same way as in the ICU setting so that the desired mean airway pressure and oxygenation are achieved with a reasonable peak airway pressure and FiO_2 . Further adjustments may be necessary in patients with acute lung injury, obesity, or other conditions that affect the ratio of the FRC to closing capacity. The latter may be particularly relevant during the performance of minimally invasive surgical procedures where abdominal insufflations may increase intra-abdominal pressure, thereby resulting in a cephalad shift of the diaphragm and a further decrease in FRC. The potential impact on such maneuvers in improving postoperative outcome has been demonstrated in the adult population (Talab et al. 2009).

Intraoperatively, the majority of patients receiving anesthesia will receive an FiO_2 that varies from 0.5 to 0.6. Although generally not necessary to maintain adequate oxygenation in patients devoid of pulmonary disease, the delivery of the volatile anesthetic agent from the vaporizer is accomplished using an FGF of 1–2 L/min which is usually equally provided by oxygen and air, both at a flow rate of 0.5–1 L/min and hence an FiO_2 of 0.5–0.6. In most scenarios, the brief exposure to such oxygen concentrations is neither helpful nor detrimental. Occasionally, provided that an acceptable oxygen saturation (93–95 %) can be maintained, the delivery of a lower oxygen concentration may be beneficial to the patient. Although there are no large, prospective trials to demonstrate such effects, it is generally accepted that the FiO_2 should be minimized in certain patient populations such as the preterm

or term neonatal who may still be at risk for the development of retinopathy of prematurity or patients with oncologic diseases who have received irradiation to the chest or chemotherapeutic regimens containing bleomycin. In such circumstances, a high intraoperative F_iO_2 should be avoided if clinically feasible. Alternatively, although the data are not conclusive, in certain patient populations such as patients undergoing major orthopedic procedures or intra-abdominal surgery, a higher intraoperative FiO_2 may decrease postoperative wound infections which is postulated to result from an increase in tissue oxygenation and improvements in oxidative killing by neutrophils (Meyhoff et al. 2009; Maragakis et al. 2009).

65.2.2 Spontaneous Ventilation

As in the ICU setting, there may be many circumstances in which spontaneous ventilation is beneficial. In the operating room setting, spontaneous ventilation is feasible during many surgical procedures which do not require neuromuscular blocking agents. Examples of such include tonsillectomy, herniorrhaphy, and most peripheral extremity surgery. When spontaneous ventilation is used intraoperatively, the airway may be controlled by mask, a supraglottic device such as an LMA, or an endotracheal tube. Regardless of the airway device used, there are several advantages of spontaneous ventilation including avoidance of the need for reversal of neuromuscular blockade, thereby decreasing the incidence of postoperative nausea and vomiting from the use of neostigmine; the addition of an additional judge of the depth of anesthesia (respiratory rate), thereby allowing the appropriate titration of intraoperative opioid therapy, a decreased risk of intraoperative awareness; as well as improvements in respiratory function by a better matching of ventilation and perfusion. Additionally, there may be specific comorbid features which mandate the maintenance of spontaneous ventilation for a variable period of time including a potentially difficult airway or an anterior mediastinal mass.

During spontaneous ventilation and the administration of various anesthetic agents, the tidal volumes may decrease from baseline values related to the effects of the anesthetic agents on the central control of ventilation or due to alterations of resistance and/or compliance induced by the airway device. In such circumstances, the new generation of anesthesia machine ventilators allows the application of pressure support to augment tidal volume of spontaneous breaths. In this setting, the pressure support above PEEP, PEEP, and inspiratory time can be set and adjusted according to the patient's response. As in the ICU setting, pressure support is triggered by the patient's change in the pressure or flow in the anesthesia circuit. In smaller children and infants, the sensitivity of the ventilator may need to be adjusted to allow for sensing of the patient's spontaneous breaths. This may be done by adjusting the flow sensitivity or the flow that the patient must generate to initiate the spontaneous breath. Alternatively, if the sensitivity is set too low, auto-triggering (inadvertent triggering of inspiratory support) may be generated by cardiac oscillations or by loss of PEEP when an uncuffed ETT is used (Sheikh et al. 2009).

65.2.3 The ICU Ventilator in the OR Including High-Frequency Techniques

In specific circumstances including comorbid respiratory disease of the patient, it may not be feasible to use a conventional anesthesia machine ventilator. In such cases, the higher working pressures and efficiency of the ICU ventilator may be required in the operating room during the anesthetic care. Alternatively, sudden changes in the intraoperative respiratory status of the patient may mandate the intraoperative switch to an ICU ventilator. In many cases, the patient can be transported to the operating room using manual ventilation and then reattached to the ICU ventilator. However, our practice includes a trial of manual ventilation which is equivalent to the transport time to the operating room before leaving the ICU setting. To accomplish this, the ICU

ventilator is disconnected, and an Ambu bag with a PEEP valve or a self-inflating resuscitation bag is used. The latter may be preferable as it allows the delivery of 100 % oxygen as well as variable levels of PEEP. Another option is to use an ICU transport ventilator, when available, as it will theoretically allow the use of the exact same pressure or volume settings as has been used in the ICU. These transport ventilators can also be used intraoperatively.

Although relatively uncommon, surgical procedures may be required on patients receiving high-frequency ventilation. As transport on these ventilators is not feasible, one of two options exists. It may be feasible to transport the patient to the operating room with usual manual ventilation and then reconnect the patient to the high-frequency ventilator. Alternatively, if the patient's condition does not permit such transport, the surgical procedure may need to be performed at the bedside in the ICU setting. Given their effects on lung movement and gas exchange, there are additional circumstances, most commonly thoracic surgical procedures, in which the use of high-frequency techniques may facilitate the surgical procedure. Both high-frequency oscillatory and jet ventilation have been used intraoperatively. Tobias and Burd reported the intraoperative use of high-frequency oscillatory ventilation (HFOV) in a cohort of 3 infants requiring surgical intervention (Tobias and Burd 2001). HFOV was used in three different clinical scenarios including its elective use to limit lung motion and facilitate thoracotomy and ligation of a patent ductus arteriosus in a preterm infant, an intraoperative switch due to progressive alterations in lung resistance and compliance leading to ineffective ventilation and oxygenation with conventional ventilation, and a neonate requiring a surgical procedure who was already receiving HFOV due to comorbid lung disease. In all cases, HFOV provided effective intraoperative ventilation and oxygenation. The intraoperative use of HFOV has also been reported to stabilize patients during surgical procedures for diaphragmatic hernia repair or the excision of thoracic lesions (bullae or congenital cystic adenomatoid malformations) (Miguet et al. 1994; Aubin et al. 1999; Nakano

et al. 1991). Likewise, there is anecdotal experience for case reports and small cases series regarding the use of intraoperative high-frequency jet ventilation (HFJV) (Cotter et al. 2004; Davis et al. 1994; Meliones et al. 1991; Schur et al. 1988; Obara et al. 1988). In a cross-over trial, where nine term infants undergoing Blalock–Taussig shunt received both conventional positive-pressure ventilation and HFJV, there was a lower mean airway pressure, higher PaO_2 , and lower PaCO_2 with HFJV (Davis et al. 1994). Additionally, as assessed by an independent observer, lung movement and the amount of surgical retraction needed were less with HFJV. In patients with Fontan physiology, HFJV resulted in a 50 % decrease in mean airway pressure, 59 % reduction in pulmonary vascular resistance, and a 25 % increase in cardiac output while providing the same ventilation and oxygenation as conventional ventilation (Meliones et al. 1991). Other authors have anecdotally reported the successful use of intraoperative jet ventilation during aortic arch surgery (coarctation repair) and resection of tracheal stenosis (Cotter et al. 2004; Schur et al. 1988; Obara et al. 1988).

The primary disadvantages to such techniques are limited availability of equipment and the unfamiliarity of pediatric anesthesia personnel with such techniques. In such circumstances, consultation with respiratory therapy staff and pediatric ICU physicians may be helpful in the successful applications of these modes of ventilation. Additionally, as these modes of ventilation eliminate the use of the anesthesia machine, the use of inhalational anesthetic agents is not feasible, thereby mandating the use of total intravenous anesthesia.

65.3 Special Situations and Adjunctive Agents in the OR

In the majority of cases in the operating room, mechanical ventilation remains straightforward with the anesthesia provider using the standard anesthesia machine and its ventilator and easily providing effective ventilation and oxygenation. In addition to issues presented by alterations in

the patient's pulmonary function, there are several other special circumstances in the operating room which may necessitate the use of specialized endotracheal tubes (one-lung ventilation) or adjunctive gases (helium, nitrogen, carbon dioxide, and nitric oxide).

65.3.1 One-Lung Ventilation

The purpose of one-lung ventilation (OLV) is to separate the two lungs, thereby allowing for the maintenance of oxygenation and ventilation through one lung while leaving the other lung deflated and motionless. The technique is used during thoracotomy and thoracoscopy to provide adequate surgical access to the lung and limit movement, thereby facilitating the surgical procedure. Occasionally the technique is used in the ICU setting in patients with unilateral lung disease to allow for selective and differential ventilation of the two lungs. For the OR setting when collapse of one lung is required, there are several options for OLV depending on the age and size of the patient. Options include a double-lumen ETT, a bronchial blocker or balloon-tipped catheter which is placed in the main stem bronchus to occlude the lung, and selective main stem intubation. As a full review of this subject matter is beyond the scope of this chapter, the reader is referred to references Hammer (2004) and Tobias (2001) for a full description of the techniques available for OLV.

In older patients, there are several manufacturer-made sizes of double-lumen ETT which can be used in patients as young as 8–10 years of age and body weight ranging from 30 to 40 kg (Fig. 65.4). Advantages of a standard double-lumen ETT are their relative ease of use, and once placed successfully, they effectively separate the two lungs, thereby preventing spillage of contents from one lung to the other. The latter is highly beneficial when dealing with empyema and infectious processes and mandatory when performing bronchoalveolar lavage. Additionally, a double-lumen ETT allows the easy and rapid switch from two-lung to one-lung ventilation as well as provides a means of differential ventilation of the two lungs. When anatomic or size constraints preclude the

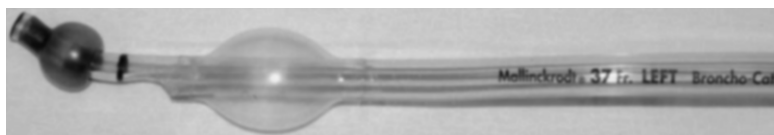


Fig. 65.4 Distal (tracheal end) of a standard double-lumen endotracheal tube used for one-lung ventilation during thoracic surgery. The tube has two lumens with

balloons which allow separation of the two lungs. The distal opening of the far tube is placed into the left main stem bronchus while the proximal opening lies in the trachea

use of a double-lumen ETT, the other two choices for OLV are selective main stem intubation or the use of a bronchial blocker. The major disadvantage of selective main stem intubation is that it is not possible to quickly change from OLV to two-lung ventilation without repositioning the ETT from the main stem bronchus into the trachea. With movement of the ETT, inadvertent extubation may occur which may be particularly problematic for the patient in the lateral decubitus position. For main stem intubation, the ETT should be 0.5 mm smaller than what would normally be used based on the patient's age (usually a 3.0–3.5 ETT in neonates). Using conventional direct laryngoscopy, the ETT is placed into the midportion of the trachea and bilateral breath sounds verified. The depth of insertion of the ETT at the alveolar ridge is noted. The ETT is then advanced into the main stem bronchus, and when there is disappearance of breath sounds on the left, the depth of insertion is noted again. This documents the depth of insertion for mid-tracheal placement and main stem bronchus placement of the ETT. The ETT is advanced only until there is a disappearance of breath sounds on the left. Placement too deep into the main stem bronchus may occlude the bronchus to the right upper lobe and prevent ventilation of that lobe. Although blind placement into the right main stem bronchus is generally feasible, left main stem intubation may be more problematic. For left-sided placement, the author recommends reversing the usual orientation of the bevel at the distal end of the ETT, using a stylet so that the concave segment is now convex. When this is done, the angle of the bevel at the distal end of the ETT will face the patient's right side with the Murphy's eye along the left lateral wall of the trachea. Once the ETT is positioned in the midportion of the

trachea, the stylet is removed to prevent tracheal trauma and the ETT advanced. Other maneuvers suggested to aid the successful placement in the left main stem bronchus include elevating the contralateral shoulder or turning the head to the opposite side. The author's preference, and perhaps the easiest technique, is to use bronchoscopic guidance by placement of the fiber-optic bronchoscope through the ETT, into the bronchus to be occluded, followed by advancement of the ETT over the bronchoscope. Advancement of the ETT using fluoroscopic guidance is also feasible if a suitable-sized bronchoscope is not available.

Alternatively, the bronchus on the operative side can be occluded with a bronchial blocker, thereby eliminating the need for manipulation of the ETT during the procedure. Several different devices can be used as bronchial blockers including the Univent endotracheal tube (Fuji Systems, Tokyo, Japan) which has a bronchial blocker incorporated into the shaft of the ETT or any balloon-tipped catheter such as a Fogarty embolectomy catheter, atrio-septostomy catheter, pulmonary artery catheter, or the Arndt endobronchial blocker (Cook Critical Care, Birmingham, In). These devices have a balloon at the end that is inflated to occlude the bronchus of the operative lung. Those with a central channel (pulmonary artery catheter, Arndt endobronchial blocker, Univent blocker) provide the advantage of allowing some degree of suctioning through the channel, not to clear the lung of secretions as the channel is too small for that purpose but rather to deflate the operative lung and improve surgical visualization. The central channel can also be used for the insufflation of oxygen and the application of CPAP should that become necessary to maintain arterial oxygenation. When devices without a central channel are used, air or gas

cannot exit from the lung once the balloon is inflated; therefore, the lung may not deflate totally and may obscure surgical visualization. Regardless of which catheter and technique of placement are chosen, there remains a risk of displacement of the bronchial blocker during the surgical procedure or with repositioning of the patient. If this occurs, the bronchial blocker may occlude the tracheal lumen just beyond the ETT, resulting in inadequate ventilation. Continuous auscultation of breath sounds on the nonoperative side and monitoring of airway pressures should identify this problem rapidly. Clinical experience suggests that inflating the balloon of the bronchial blocker with saline as opposed to air may limit movement and dislodgement during surgical manipulation.

After separation of the nonoperative from the operative lung using one of the above described techniques, general anesthesia is maintained with a combination of intravenous and inhalational anesthetic agents. Hypoxic pulmonary vasoconstriction (HPV) is a normal physiologic response that occurs in poorly ventilated alveoli to preferentially shunt pulmonary blood flow to ventilated alveoli. Any nonspecific vasodilator (terbutaline, albuterol, isoproterenol, dobutamine, nicardipine, nitroglycerin, sodium nitroprusside, inhalational anesthetic agent) can impair HPV and affect oxygenation. The anesthetic technique can also affect HPV and thereby arterial saturation. Isoflurane, sevoflurane, or desflurane has less of an effect on HPV than either halothane or enflurane (Benumof et al. 1987; Wang et al. 2000). During the procedure and OLV, ventilation is maintained with tidal volumes of 6–8 mL/kg, provided that the peak inflating pressure can be maintained at ≤ 30 cmH₂O and the respiratory rate adjusted as needed to maintain normocarbida as hypocarbida interferes with HPV. In the adult population, tidal volumes are better maintained with lower peak inflating pressures with pressure-limited rather than volume-limited ventilation. Although ventilation is generally easily maintained, given the large area of lung that is excluded for gas exchange, oxygenation may be problematic especially in patients with comorbid respiratory problems. If adequate oxygenation

cannot be maintained during OLV with an FiO₂ of 1.0 to the nonoperative side, CPAP of 4–5 cmH₂O can be applied to the operative lung provided that a DLT, Univent, or bronchial blocker with a central channel has been used. Although this will improve oxygenation, it may also distend the operative lung to some degree and impair surgical visualization. If the above measures fail, it may be necessary to provide two-lung ventilation intermittently. Alternatively, oxygenation can be improved by the administration of nitric oxide or a direct acting, α -adrenergic agonist (Moutafis et al. 1999; Dietrich and Tobias 2003). The latter is thought to act by its augmentation of HPV.

65.3.2 Helium

The therapeutic benefits and clinical applications of helium–oxygen gas mixtures were first reported over 70 years ago (Barach and Eckman 1935, 1936). In current clinical practice, a helium–oxygen combination is most commonly used to improve gas exchange in patients with upper airway obstruction of various etiologies, including infectious and post-intubation croup (Tobias 1997; Berkenbosch et al. 2004; Duncan 1979). The beneficial effects of helium have also been noted and reported in patients with obstructive processes more distally along the tracheobronchial tree such as those who require mechanical ventilation for asthma and other respiratory disorders (Manthous et al. 1997; Michael et al. 1999). Additionally, there are anecdotal reports of helium being used successfully in the operating room to treat respiratory compromise related to an anterior mediastinal mass, bronchospasm, and tracheal stenosis.

There are several potential benefits of helium in patients with obstructive diseases at various points along the airway. Helium's primary effects are the result of its lower density, thereby providing decreased resistance during turbulent gas flow. Resistance during turbulent gas flow, as described by the Hagen–Poiseuille law, is directly related to the density of the gas. Helium may also increase gas flow by converting turbulent flow to laminar flow by lowering the Reynolds number.

The Reynolds number is the ratio of kinetic and viscous forces. It predicts whether flow will be laminar or turbulent (turbulent flow occurs with a Reynolds number $\geq 2,000$). Helium also enhances the diffusion effect on the elimination of CO_2 . Through a mixture of helium–oxygen, carbon dioxide diffuses four- to fivefold faster than nitrogen–oxygen. Therefore, for the equivalent partial pressure of CO_2 , a greater amount of CO_2 is eliminated per unit of time. In the perioperative setting, helium is used most commonly for the induction of anesthesia in patients with upper airway obstruction such as croup or epiglottitis who are presenting to the operating room for direct laryngoscopy under general anesthesia. In this scenario, a mixture of helium and oxygen is used to deliver increasing concentrations of sevoflurane while maintaining spontaneous ventilation. As one of the factors that determine the rapidity of anesthetic induction is minute ventilation, the addition of helium may augment minute ventilation especially in the presence of upper airway obstruction. Additionally, helium may be used intraoperatively during airway laser surgery to decrease the risk of airway fire as helium has a higher conductivity of heat than a nitrogen–oxygen mixture.

In the pediatric ICU setting, helium is generally delivered using a high flow gas system to eliminate the entrainment of room air. Alternatively, there are also mechanisms to allow its delivery through an ICU ventilator. In the OR setting, helium can be delivered with an anesthesia machine that is commercially available with a helium flow meter in addition to the standard anesthesia gases (oxygen, air, and nitrous oxide). These machines allow the administration of helium from an E cylinder (generally one containing 80 % helium and 20 % oxygen) prior to the gas flowing through the vaporizers. Therefore, no specialized setup or preparation is required for the delivery of helium. Of importance is the fact that the helium flow meter does not participate in the ratio control (proportioning system) that is present with the use of nitrous oxide and oxygen. Therefore, when helium is in use, the delivery of a hypoxic mixture is possible. Therefore, it is mandatory to use a separate in-line oxygen and

anesthesia gas monitor as well as standard ASA monitors.

65.3.3 Nitric Oxide, Carbon Dioxide, and Nitrogen

In patients with congenital heart disease or pulmonary hypertension, supplemental gases such as nitric oxide (NO), carbon dioxide, or nitrogen may be added to the inspiratory gas mixture to manipulate the pulmonary artery pressure. NO is used primarily in the treatment of pulmonary hypertension. Its mechanism of action resides in its ability to stimulate guanylate cyclase, thereby increasing the concentration of cGMP. As it is delivered via the lungs, its effect is limited to the pulmonary vasculature as it is inactivated after interaction with hemoglobin. In the perioperative care of infants with single-ventricle anatomy, the ratio of system to pulmonary vascular resistance is a key factor in the regulation of systemic blood flow and oxygen delivery (Norwood 1991). In addition to pharmacologic therapy, the control of the partial pressure of oxygen and/or carbon dioxide in the blood has been shown to be an effective means of altering the ratio of pulmonary to systemic vascular resistance and thereby controlling systemic oxygen delivery (Jobes et al. 1992). Methods to control the partial pressure of oxygen and carbon dioxide in the blood include the either use of a subatmospheric concentration of oxygen or the addition of carbon dioxide to induce hypercapnia. Although there are proponents to both therapies, it has been demonstrated that hypercapnia increases cerebral oxygenation, mean arterial pressure, and systemic oxygen delivery, while lowering the fraction of inspired oxygen has no effect (Ramamoorthy et al. 2002).

In clinical ICU care, these adjunct gases are frequently added to the inspiratory limb of the respiratory circuit with the flow rates adjusted to achieve the desired concentration. In distinction to mechanical ventilation in the ICU setting, in the OR, there is generally at least partial rebreathing of the exhaled gases (see above) during the use of a circle system. This rebreathing can result in the administration of a higher concentration of

one of the adjunct gases (nitric oxide, carbon dioxide, or nitrogen) than is intended (Tobias and Grueber 2000). One means of eliminating such concerns is to use an ICU ventilator for such cases. However, if the anesthesia machine ventilator is used, the FGF rate should equal at least and preferably twice the minute ventilation (Tobias and Grueber 2000). This will eliminate rebreathing and the issues outlined above.

65.4 Summary

As in the ICU setting, ventilatory support is frequently required in the operating room during the provision of general anesthesia. In distinction to the ICU setting, many patients who receive endotracheal intubation and mechanical ventilation in the operating room have relatively normal pulmonary function and thereby require minimal support. In many of these patients, mechanical ventilation is required due to the requirements for the surgical procedure, the depressant effects of the anesthetic agents, or the use of neuromuscular blocking agents. However, significant respiratory comorbidities may exist in patients requiring general anesthesia which mandate significant expertise in mechanical ventilation to provide adequate intraoperative oxygenation and ventilation. In the majority of cases, mechanical ventilation is provided by the use of the anesthesia machine and its ventilator. As in the ICU setting, the basic settings for mechanical ventilation include the provision of adequate minute ventilation (respiratory rate and tidal volume) and the maintenance of oxygenation through manipulations of the mean airway pressure (PEEP, PIP, and inspiratory time) and FiO_2 . Ventilation may be provided by pressure- or volume-limited modes with manipulations of the inspiratory time to compensate for changes in respiratory compliance and resistance. Additionally, during many surgical procedures, spontaneous ventilation is maintained and supported by pressure support which is now available on modern-day anesthesia machines. Rarely, patient comorbidities or specific requirements for the surgical procedure preclude the use of the anesthesia machine ventilator

and mandate the use of an ICU ventilator. In such circumstances, anesthesia is provided by the use of intravenous agents. Additionally, other modes of respiratory support such as high-frequency ventilation may be required during anesthetic care, and with appropriate preparation, such techniques can be used intraoperatively. In special circumstances, adjunctive agents such as helium, nitric oxide, nitrogen, or carbon dioxide may be used based on the patient's status. Regardless of the technique chosen, a thorough preoperative evaluation which includes an investigation into the patient's current respiratory status is mandatory to ensure the appropriate intraoperative care of respiratory function and to ensure adequate oxygenation and ventilation.

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Part XXVI

Extracorporeal Membrane Oxygenation in Acute Hypoxemic Respiratory Failure

Extracorporeal Membrane Oxygenation in Acute Hypoxic Respiratory Failure

66

Desmond Bohn

Educational Aims

- To provide a historical background on the use of ECMO in AHRF in neonates and older children
- To describe the technology available, cannulation techniques, oxygenators, pump flows, and weaning from ECMO support
- To outline the indications and contraindications for ECMO initiation in AHRF
- To describe the outcomes in neonatal and pediatric ECMO use
- To describe newer innovations in extracorporeal pulmonary support including pumpless CO₂ removal

extended the safe period for cardiopulmonary bypass. It was a matter of time therefore before this technology migrated from the operating room to the ICU to support patients dying of hypoxemia who could not be ventilated. In 1970, Baffes used extracorporeal support in children with congenital heart disease after open heart surgery (Baffes et al. 1970). The first successful use of a membrane oxygenator to support a patient with acute hypoxic respiratory failure (AHRF) was published in 1972 using the Bramson lung (Hill et al. 1972). Following the publication of further case series (Gille and Bagniewski 1976), an NIH-sponsored randomized trial was set up in 1975 to compare the use of veno-venous (V-V) ECMO in ARDS with what was then standard-of-care positive-pressure ventilation (Zapol et al. 1979). The entry criteria were modest by today's standards (FiO₂ 0.6, PEEP ≥6 cmH₂O for 2 h or more). Ninety patients were randomized, but the disappointing survival of 10 % in both arms of this study led to ECMO being largely abandoned as a treatment for AHRF in adults in North America. Bartlett, who was a lead investigator in the trial, then pioneered the use of ECMO in neonatal respiratory failure and published the first case series of 45 patients from the University of Michigan in 1982 with a 50 % survival (Bartlett et al. 1982). He set up the Extracorporeal Life Support Organization (ELSO), and the Registry now contains a database of over 30,000 patients where ECMO has been used for either pulmonary or cardiac support. Over 25,000 neonates with AHRF have been treated with an overall

66.1 Historical Background

The development of the membrane oxygenator for the use in open heart surgery in the late 1960s was a major advance in cardiopulmonary bypass technology. Compared with the previous generation of bubble oxygenators, these devices were much less destructive of blood components and

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survival of 80 %. Beginning in the late 1980s, an increasing number of pediatric patients outside the newborn period with respiratory failure unresponsive to conventional treatments have had ECMO used as a rescue therapy. Reports from the Registry show data on over 3,000 patients with an overall survival of 60 % (ELSO Registry 2010).

66.2 ECMO: Cannulation, Pumps, and Oxygenators

The original experience in adults was with V-V ECMO using cannulas in the neck and groin. In neonates the femoral vein is too small for cannulation so the first series accessed the circulation via the right internal jugular vein to the right atrium for venous drainage and returned oxygenated blood to the aorta via the carotid artery (V-A ECMO). With the development of double-lumen venous cannulas, supporting oxygenation without arterial cannulation became an option as long as cardiac function was adequate (V-V ECMO). These cannulas have a large end hole and multiple side holes for venous drainage, and oxygenated blood is returned through side holes in the cannula which are orientated so that blood flows towards the tricuspid valve to minimize recirculation. Double-lumen cannulas are now available in up to 18F size and are capable of providing enough flow to support children of up to 10–12 kg. In larger children where the V-V mode is chosen, a double venous cannulation is performed accessing the right atrium via the right internal jugular vein with a second cannula inserted into the IVC via the femoral vein. In a large series from the University of Michigan, V-V support was successfully used in 53/128 pediatric patients with AHRF, while a further 11 had to be converted from V-V to V-A (Swaniker et al. 2000). A very recent innovation has been the development of the Avalon Elite™ bicaval double-lumen cannula for V-V support in both adults and children which has a high profile and can deliver high flows with little recirculation.

An alternative technique of using the extracorporeal circuit at lower flows to remove CO₂ while using a low ventilatory rate with high end-expiratory pressure to provide oxygenation (ECCO₂R) (Gattinoni et al. 1986).

The roller pump has been used for the majority of ECMO support up until 2000. The system relies on gravity to enhance venous return and also requires a reservoir to avoid negative pressures in the venous side. A servo-regulated bladder is incorporated into the circuit. More recently more centers are using a centrifugal pump system which does not require a venous reservoir, and the circuit can be rapidly primed and deployed in an emergency situation for cardiac support. Flow is generated via a spinning rotor in the pump head which generates a negative pressure in the venous line. Many centers have been reluctant to use this system in the past because of concerns over increased hemolysis induced by the high negative pressure created in the pre-membrane part of the circuit. However, improvements in pump head technology have eliminated this problem. The newer generation of centrifugal pumps (Jostra Rotaflow, Levitronix CentriMag) have seen further improvements in technology, and their compact design makes them ideal for use in transport.

The silastic membrane oxygenator has been an integral part of all pediatric ECMO circuits for the past 25 years. However, reliable and robust as it undoubtedly is, it has a high resistance and there is a substantial pressure differential between the venous and arterial side of the circuit. The introduction of microporous hollow fiber membranes resulted in increased efficiency and allowed for the complete circuit to be heparin bonded, but plasma leakage resulted in foam forming around the oxygenator and limited the duration of usage. Newer generation hollow fiber polymethylpentene oxygenators such as the Maquet Quadrox have demonstrated improved efficiency without plasma leakage (Khoshbin et al. 2005). Their small priming volume and low resistance make them ideal for both emergency deployment and long-term use.

66.3 ECMO Patient Management: Pump Flow, Ventilator Settings, Anticoagulation, and Fluids

Pump flows for supporting neonates with AHRF are set to deliver 100–120 ml/kg/min sufficient to keep the $\text{SaO}_2 > 90\%$ and SvO_2 at 70–75 % on V-A bypass or a SaO_2 of 85–90 % on V-V. In children outside the newborn period, pump flows of 80–100 ml/kg/min are usually sufficient to achieve these objectives. The hematocrit should be maintained at 40–45 % to maximize oxygen delivery. The sweep gas flow is adjusted to achieve a PaCO_2 of 40–45 mmHg, avoiding alkaline pHs especially in newborn infants. The key objective of ECMO is to provide lung rest by removing the ongoing injury to the lung from positive pressure and oxygen. The peak inspiratory pressure on ventilator should be reduced to < 25 cmH₂O and the rate to 5–10 breaths/min. PEEP at a level of 8–12 cmH₂O is added in an attempt to prevent further derecruitment. Patients may also be turned into the prone position (Haefner et al. 2003).

Maintaining adequate anticoagulation in patients on ECMO is a fine balance between preventing thrombus developing in the circuit and not causing bleeding, especially in the central nervous system, the major complication in newborns. Heparin is infused at a rate of 20–50 units/kg/h with the objective of maintaining the activated clotting time (ACT) at 180–200 s. In the event of bleeding, the ACT target can be reduced to 160–180 s. Platelets are infused to maintain the count above 100,000/mm (Gille and Bagniewski 1976) in newborns. Both aminocaproic acid (Amicar) and activated factor VIIa have been used to treat hemorrhage in ECMO patients (Dominguez et al. 2005; Horwitz et al. 1998; Niebler et al. 2010) but are not without risk of inducing circuit thrombosis (Dominguez and Brown 2010).

The management of fluid balance has been shown to affect the outcome in ECMO patients.

Failure to return the patient to dry weight has been associated with non-survival in a large series of ECMO support for pediatric AHRF (Swaniker et al. 2000). Therefore, diuresis should be maintained with a furosemide infusion or, if that fails, hemofiltration. At the same time it is important that patients receive nutritional support to prevent protein breakdown, negative nitrogen balance, and tissue edema. Enteral feeding is the preferred option to prevent bacterial translocation from the gut (Pettignano et al. 1998).

66.4 Weaning from ECMO and Decannulation

Following the initiation of ECMO, the systemic inflammatory response associated with the exposure of blood to the oxygenator and circuit results in diffuse capillary leak and worsening edema of the injured lung. There is a further reduction in pulmonary compliance and opacification of the chest x-ray. Signs of improvement in lung function indicating that an attempt at weaning from ECMO may be feasible include the onset of diuresis, an increase in lung compliance, and clearing of the chest x-ray. In pediatric AHRF this rarely occurs within the first week of support (Swaniker et al. 2000), but in neonates with meconium aspiration it may be as little as 3 or 4 days. In patients on V-A support, positive pressure is increased to regular settings and then flows are reduced while observing the SaO_2 . The final test is to clamp the cannulas and circulate flow through the bridge, while the patient is on full ventilation. The heparin infusion must be switched from the circuit to the patient and cannulas unclamped and flushed at regular intervals while this is happening. For patients on V-V bypass, the lung can be tested by switching off the sweep gas to the oxygenator, while fully ventilating the patient. ECMO can be discontinued and the patient decannulated if a $\text{SaO}_2 > 85\%$ can be maintained on an $\text{FiO}_2 \leq 0.6$ and a PEEP ≤ 10 cmH₂O.

66.5 ECMO for Acute Hypoxic Respiratory Failure

66.5.1 Indications and Contraindications

Indications for the initiation of ECMO support for AHRF in neonates are those cannot be oxygenated by either conventional mechanical ventilation (CMV) or a mode of high-frequency ventilation (HFOV or HFJV) and have failed to respond to inhaled nitric oxide (iNO). For infants with lung disease of prematurity, the algorithm would also include the use of surfactant replacement therapy. Historically failure to respond with a high risk of mortality has been defined based on the use of the oxygenation index (OI), which incorporates the PaO_2 , FiO_2 , and a measurement of the intensity of ventilation, namely, the mean airway pressure ($\text{OI} = \text{MAP} \times \text{FiO}_2 \times 100 / \text{PaO}_2$). However, this number may exaggerate the severity of the oxygenation defect in infants with a right-to-left shunt at ductal level where the OI is calculated from umbilical arterial PaO_2 measurements. Neonates whose OI exceeds 40 are predicted to have a greater than 80 % mortality, and this number has been used to enter patients in a number of prospective trials of alternative therapies in AHRF as well as the 3 RCTs which have compared the outcome of ECMO with conventional ventilation (UK Collaborative ECMO Trial Group 1996; Bartlett et al. 1985; O'Rourke et al. 1989). It is widely accepted that an OI of >40 on three measurements 4–12 h apart is a robust indication for ECMO. However, with the increased use of high-frequency ventilation and iNO, many infants can improve temporarily which may delay them being referred for ECMO. Given that several studies have shown that the outcomes are less good with longer duration of pre-ECMO therapy, this has led to the suggestion that an OI of >25 should be used as an indication in this situation.

The indications for ECMO are less clearly defined in older children, particularly those

with ARDS, which is a multisystem disease frequently involving other organ systems apart from the lungs. However, recent studies have shown that there is a relationship between both OI and the PaO_2 to FiO_2 ratio (P/F) and both the duration of ventilation and outcome in children with AHRF outside the newborn period (Flori et al. 2005; Trachsel et al. 2005). It can be stated with a fair degree of certainty that in a child with single-system lung disease, an OI of >25 that is continuing to rise with no response to alternative strategies, which would include HFOV, prone position, iNO, and perhaps surfactant, should be considered for ECMO, unless there are contraindications.

The generally accepted contraindications for the institution of ECMO in any age group include greater than 10 days of positive-pressure ventilation, an irreversible underlying disease process, and major central nervous system abnormalities or hemorrhage. Patients with diseases associated with an uncorrectable coagulopathy are usually excluded because of the risk of hemorrhage. In the past, immunosuppressed pediatric patients with underlying malignancies were excluded, but with some survivors being reported this is also being rethought. In the case of neonatal ECMO, patients who are less than 34 weeks gestation or <2 kg birth weight are also generally excluded because of the risk of intraventricular hemorrhage associated with prematurity. As pump and circuit technology improves leading to a reduction in adverse patient outcomes, some of these contraindications may be thought of as relative rather than absolute.

66.5.2 Complications

With a highly invasive complex technology such as ECMO, complications can be expected. These can be categorized into patient and device related (Tables 66.1 and 66.2).

Table 66.1 Principal technical (device) complications

Complication	Comments
Oxygenator failure	It is unusual for an oxygenator to fail completely, but they do lose efficiency over time
Pump tubing (raceway) rupture	Only in the roller pump system
Unfavorable cannula position	More common with the venous cannula. Leads to high negative pressures and inadequate flows especially with centrifugal pumps
Circuit thrombus formation	May occur in oxygenator, bridge, and bladder of hemofilter
Air embolism	Can occur if there are cracks in the tube or through stopcocks. There is a high negative pressure in the venous line pre-oxygenator of centrifugal pumps
Pump failure	A rare event. Pumps have a battery backup system which can also be used for transport. There is also a hand crank option
Hemolysis	Formerly a significant problem with the centrifugal pump system. Much less of a problem with the newer pump heads

Table 66.2 Principal patient complications

Complication	Comments
Seizures and other CNS complications	May be caused by intracerebral hemorrhage or infarction. Commonly manifested by the onset of seizures
Systemic hypertension	May be a predisposing factor to above. Systemic hypertension is seen frequently when pump flow is initiated
Renal dysfunction and fluid overload	The development of renal failure or the inability to maintain patient within 10 % of dry weight has been negatively correlated with outcome (Swaniker et al. 2000)
Culture-proven infection	Can be seen in up to 12 % of patients (Bizzarro et al. 2011)
Hepatic failure and hyperbilirubinemia	Hepatic failure developing on ECMO is associated with poor outcome (Swaniker et al. 2000)
Failure to separate from ECMO	Failure of lung recovery and major neurological damage are the most common reasons

66.5.3 Outcome in ECMO Support for AHRF

The survival to separation from ECMO in over 24,000 patients placed with AHRF in the newborn period is 85 % in the ELSO Registry with 75 % survival to hospital discharge (ELSO Registry 2010) (Fig. 66.1). Within this large group with various etiologies, the survival is best in meconium aspiration syndrome (>90 %) and worst in congenital diaphragmatic hernia (60 %). The other noticeable trend in the Registry data over the past 5 years has been the decrease in number of neonatal patients where ECMO has been used as a rescue therapy. This is partly due to the increased use of alternate therapies such as iNO and high-frequency ventilation but also due in large part to an alteration in ventilation practices, principally abandoning the use of hyperventilation to reverse ductal shunting. While peak airway pressures of over 40 cmH₂O were commonly seen in patients referred for ECMO, there has been a significant reduction in this past decade with the increasing recognition of ventilation-induced lung injury (Roy et al. 2000). A convincing argument can be made that very high numbers of these patients being put on ECMO in the 1990s were being rescued from ventilation-induced lung injury rather than underlying lung disease. However, widespread adoption of these alternate therapies is not without hazard in that when these fail to improve the oxygenation, sicker infants require transfer to an ECMO center, although this has not been reflected in an increase in mortality (Fliman et al. 2006). The argument as to whether ECMO improves the outcome in severe AHRF in newborns has been addressed in three randomized trials. Two of these were criticized because of lack of equipoise in the study sites (Bartlett et al. 1985; O'Rourke et al. 1989). The third was performed in the UK where 55 referral centers randomized 185 patients to either conventional management or transfer to one of five ECMO centers. The primary end point was survival without disability at 1 year. The study was stopped early because of favorable outcome in the ECMO group (UK Collaborative ECMO Trial Group 1996).

Fig. 66.1 Neonatal diagnoses and survival (ELSO Registry (2010); reproduced with permission)

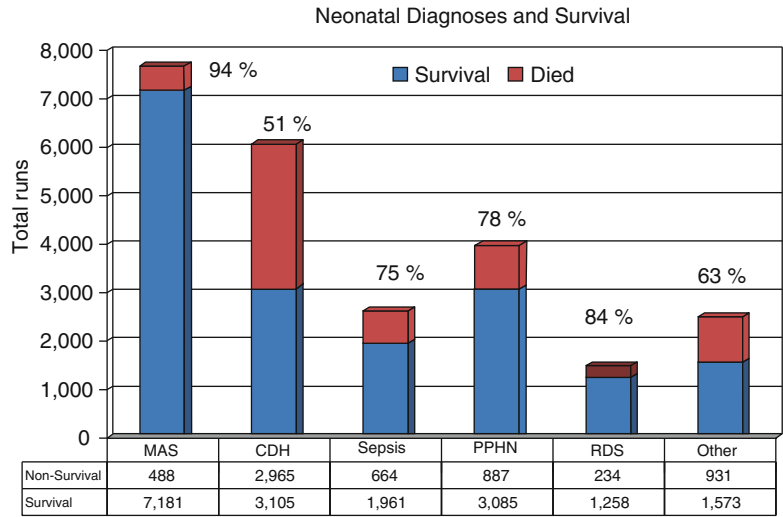
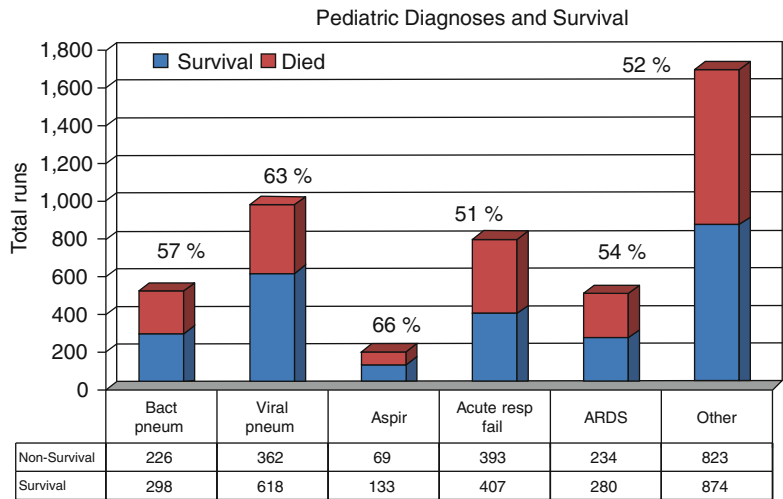


Fig. 66.2 Pediatric diagnoses and survival (ELSO Registry (2010); reproduced with permission)



The outcome in the over 4,000 children outside the newborn period reported to ELSO is different with 65 % being successfully separated from ECMO and 56 % surviving to hospital discharge (ELSO Registry 2010) (Fig. 66.2). The average duration of support was 10 days with occasional very prolonged runs of up to 3 months. The fact that the outcome is not as good as the neonatal patients is not surprising given the fact that in the former group the majority of patients have single-system pulmonary disease while older children frequently have multisystem disease.

The largest published single center experience is from the University of Michigan which

reported 77 % survival in 128 patients between 1985 and 1998 (Swaniker et al. 2000). The mean duration of support in this series was 12 ± 10 days (median 9.5) with a range of 0.2–47 days. A similar outcome was reported from Atlanta in 63 patients between 1991 and 2002 (Pettignano et al. 2003). The underlying disease process has an impact on outcome with the highest survival in patients with viral pneumonia in the ELSO Registry. Within this category, Moler et al. (1993) reported a 49 % survival of patients with RSV, although this series was published more than 10 years ago since ventilation practices have changed substantially. A more recent series

of ex-premature infants with RSV showed an 80 % survival to hospital discharge, but with a 60 % neurodisability rate (Brown et al. 2004). Good outcomes have been reported in small case series for pulmonary hemorrhage (Kolovos et al. 2002; Siden et al. 1994), burns and smoke inhalation (Goretsky et al. 1995; Kane et al. 1999; Leesin et al. 1996; Pierre et al. 1998), posttraumatic lung injury (Fortenberry et al. 2003), and occasional patients with severe asthma and hypercarbia (Hebbar et al. 2009). Two disease categories remain particularly challenging. AHRF secondary to pertussis that presents in the first 3 months of life is associated with a particularly severe form of pulmonary hypertension which does not resolve. The mortality in these patients even with ECMO support is 80 % (Halasa et al. 2003; Pooboni et al. 2003). The second group is those patients with hematological malignancies. Data from the ELSO Registry on patients placed on ECMO following bone marrow transplantation published up to 2006 showed only one survivor to hospital discharge in 19 patients (Gow et al. 2006). For children with immunosuppression, the mortality is higher than in immunocompetent patients reported to ELSO (Gupta et al. 2008) but there are some small case series with good outcomes. Linden reported 3/4 children with pneumocystis pneumonia surviving (Linden et al. 1999) and 2/4 survivors in children with leukemia and ARDS in a second series (Meister et al. 2010). As can be anticipated the cost of ECMO in financial terms is significant. Vats (Vats et al. 1998) has computed the hospital costs to be \$200,000 which translates into \$4,190/life-year.

The efficacy of ECMO as a lifesaving therapy in neonatal AHRF has a sound basis supported by a high level of evidence. The case is more difficult to make in older children in the absence of any randomized trial evidence. The only attempt at such a study was abandoned because with a change in ventilation practice, the predicted mortality was substantially less than the actual (Fackler et al. 1997). There is however a large amount of evidence from case series and Registry data which supports its use. In a multi-institutional retrospective cohort analysis of over 300 patients with AHRF from 32 centers over a 1-year period

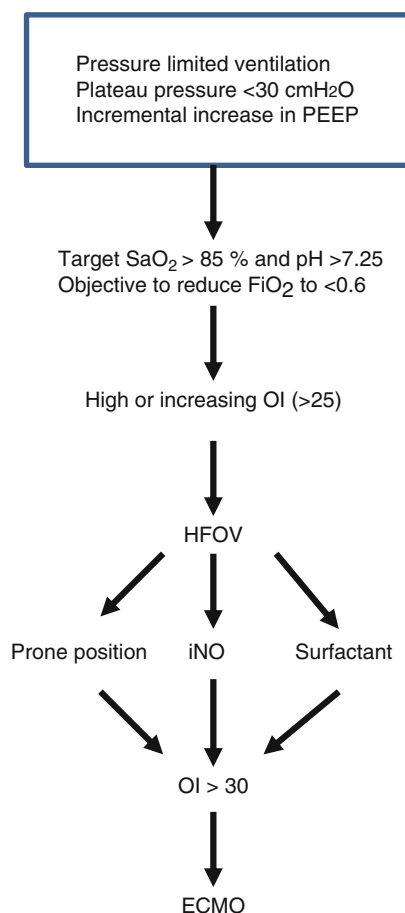


Fig. 66.3 Algorithm for severe AHRF

in an era before the use of lung-protective ventilation, ECMO was associated with reduced mortality in the group of patients with the highest OI compared with those that received conventional or high-frequency ventilation (Green et al. 1996). However, even in an era of lung-protective ventilation and widespread use of high-frequency ventilation, children who are impossible to oxygenate can be saved by having access to ECMO. This was illustrated in the 2009–2010 H1N1 epidemic where 103 patients <20 years of age were put on ECMO with a 48 % survival (<http://www.elseo.umich.edu/H1N1Registry>). The question arises as to what defines a failure of conventional therapy as a prelude to ECMO. Options will be influenced by published literature but also by physician bias. Figure 66.3 provides an outline of an algorithm for clinical decision making in such a scenario.

66.6 Extracorporeal Pulmonary Support: Future Directions

The major advances in technology that have occurred in the past 20 years have led to innovative thinking of the application of extracorporeal support in severe AHRF. The compact design of pumps and oxygenators has made transport on ECMO a reality rather than a novel event that requires prolonged planning and major consumption of resources (Clement et al. 2010; Prodhan et al. 2010; Coppola et al. 2008). This notwithstanding, ECMO is a complex, labor-intensive system with attendant risks. One of the newer innovations has been the introduction of a pumpless system for extracorporeal CO₂ removal in patients with AHRF where hypercarbia is a feature. Considerable experience has now accumulated with the Novalung where patients are cannulated by A-V access through femoral artery and vein, and the device is perfused by systemic pressure with sufficient flow to remove CO₂ and partially support oxygenation (Florchinger et al. 2008; Zimmermann et al. 2009; Weber-Carstens et al. 2009). In situations where flow is insufficient, a pump can be added to the circuit. Pediatric experience is this device is limited so far, but there are case reports of it being used successfully in patients with asthma and severe hypercarbia (Romano 2007; Conrad et al. 2007). It is being used increasingly as a bridge to lung transplantation in patients with cystic fibrosis and primary pulmonary hypertension (Fischer et al. 2007; Ricci et al. 2010). In this situation hypercarbia is often associated with such severe right ventricular dysfunction and limitation of pulmonary blood flow that effective removal of CO₂ can only be achieved with transpulmonary placement of the device (pulmonary artery to pulmonary vein) (Strueber et al. 2009).

Essentials to Remember

- ECMO is the ultimate high-tech modality for the support of respiratory failure in critical care. While the technology has improved significantly in the past 20 years, the survival outside the newborn period is still only 50 % and the complications are significant.

- Pulmonary failure is usually a single-system disease in the newborn, while it is frequently part of a multiorgan dysfunction syndrome in older children. Hence, the outcomes will be less good.
- As technology improves and the complication rate falls, more children previously deemed ineligible will be considered for ECMO.
- Pumpless extracorporeal CO₂ removal is a very useful modality as a bridge to transplantation in patients with severe hypercarbia due to pulmonary vascular disease and right heart dysfunction.

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Part XXVII

Evaluating Mechanical Ventilators for Use in Neonatal and Pediatric Patients

Evaluating Mechanical Ventilators for Use in Neonatal and Pediatric Patients

67

John Salyer

Once technology is master, we shall reach disaster, faster.

.....Piet Hein¹

Educational Goals

- Understand the essential features and capabilities of a neonatal-pediatric mechanical ventilator
- Describe the importance of bench and clinical testing of mechanical ventilators as part of purchase decision
- Describe how to construct a bench evaluation of a mechanical ventilator to be used in neonatal and pediatric patients
- Describe how to construct a clinical evaluation of a mechanical ventilator to be used in neonatal and pediatric patients
- Understand the importance of, and methods for, accurate tidal volume measurement in neonatal and pediatric patients

It is widely acknowledged that the advancement of complex technology has been a major contributor to the rising costs of health care (Bodenheimer 2005; Ginsburg 2004). Yet, in

some cases, it is not entirely clear that we are getting a reasonable return on our investment in all this gadgetry. It is inarguable that amazing technological advances have taken place in many fields. There is evidence that this technology has been one of the factors that has contributed to improved outcomes in the care of premature infants (Fig. 67.1) (Meadow et al. 2004).

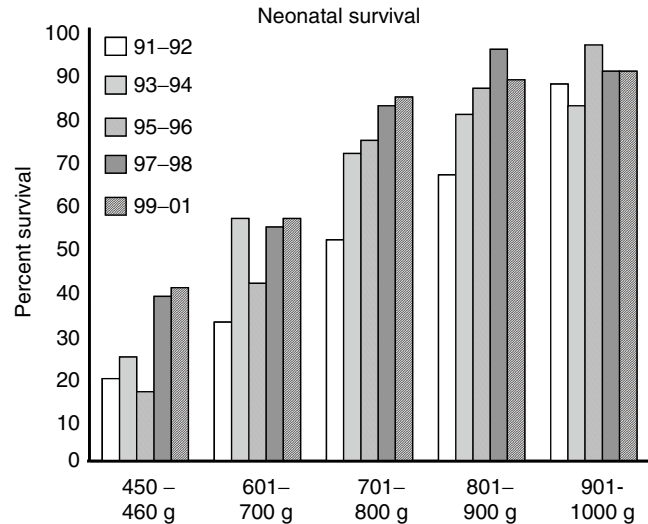
All technology is not created equal. We have often been forced to use devices and instruments in neonatal and pediatric intensive care that have been designed for adult populations. As an example, some ventilators widely used in neonatal and pediatric populations cannot accurately measure tidal volume in the neonatal- and pediatric-sized patients (Cannon et al. 2000; Castle et al. 2002; Neve et al. 2003; Salyer and Jackson 2005a). These measurement limitations are often not well understood by the clinicians who assume the displayed tidal volumes are accurate. Even among ventilators that have been designed and marketed as neonatal devices, we have demonstrated important differences in the accuracy of tidal volume measurements (Crotwell et al. 2007; DiBlasi et al. 2007).

There is now a dizzying array of modes and features that festoon newer models of ventilators (Branson and Johannigman 2004). In the spirit of

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¹Piet Hein (1905–1996) was a Dutch scientist, mathematician, and sage best known for his witty aphorisms. My favorite Hein quote is, “Men, said the Devil, are good to their brothers: they don’t want to mend their own ways, but each other’s.”

Fig. 67.1 Improvement in neonatal outcomes (Adapted from Meadow et al. (2004))



closing the gate after the cows have gotten out, we have watched as very little evidence has been developed demonstrating any effect on outcomes of ventilation related to any of these modes (Branson and Johannigman 2004). One exception to this might be the use of early intervention high-frequency oscillatory (HFOV), which has been extensively tested. But the literature on the effect of this technology remains divergent (Courtney et al. 2002; Johnson et al. 2002). A recent Cochrane review found only a minor benefit of elective HFOV (Henderson-Smart et al. 2007). These findings are probably related to heterogeneity between populations studied (Van Kaam and Rimensberger 2007).²

I believe we have a fiduciary responsibility to the communities we serve to be good stewards of the resources they give us. One important way to prosecute this responsibility is to be careful not to promote unproven technology and to carefully evaluate the performance claims of technology we are considering buying. As an industry we do not have a good track record of critically evaluating the claims of device manufacturers.

I know of hospitals that replaced their older fleets of perfectly good, time-cycled, pressure-limited neonatal ventilators for newer, allegedly sophisticated, and certainly more complex ventilators based largely on the promise of a benefit to patients of volume measurement and dual-control modes of ventilation. But, in many cases, these hospitals went on to use these newer, more expensive, and more complex ventilators in the way that they were most accustomed to: notably in time-cycled, pressure-limited modes. Had they bothered to do the most rudimentary bench testing, they would have learned that the neonatal volume measurement claims of these devices were bogus. And without accurate measurements of tidal volume, dual-control modes of ventilation aren't going to do you a whole lot of good in neonatal and pediatric ventilation.

67.1 Ventilator Efficacy, Efficiency, and Effectiveness

Mechanical ventilators are marketed in much the same way as are automobiles and refrigerators. You will be told in subtle and not so subtle ways that this new technology will benefit your patients, or save you money, or make your clinical job easier. As you ponder what you have been told, you might want to analyze this submission within the context of the three E's: efficacy, effectiveness, and efficiency (Brook and Lohr 1985).

²In the two papers cited, both published in the same issue of the *New England Journal of Medicine*, you had differing results of randomized trials to establish the salutary effect of early intervention HFOV on neonatal outcomes. HFOV use varies widely with some centers practicing early intervention with HFOV for most infants with RDS, while other centers use very little HFOV, reserving it for only the most extreme rescue applications.

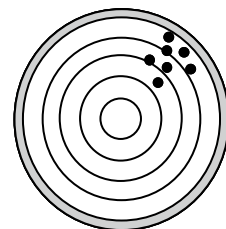
This terminology is used by researchers who conduct health technology assessment. These terms have some “classical” definitions in terms of evaluating technology. They are:

- *Efficacy* can be defined as the probability of a medical technology or intervention to achieve its desired effect under ideal conditions, such as a bench test or in vitro studies.
- *Effectiveness* is the performance of a medical device or intervention under ordinary, rather than ideal, conditions. Differences in the skill of clinicians and innumerable other conditions may mean that the technology does not perform as well in the real world of clinical practice as it did under ideal circumstances. This is particularly important when considering neonatal and pediatric mechanical ventilator performance. The accurate measurement of very small tidal volumes requires the use of proximal flow sensors between the ventilator circuit and the endotracheal tube.³ While bench testing of these sensors (efficacy) generally yields clinically acceptable accuracy, the performance of the sensors in the real clinical environment is never as good as on the bench. The sensors’ performance deteriorates in a humid environment because of condensation, and the sensors can get contaminated with secretions and particulate matter that the patients exhale.
- *Efficiency* describes the combination of effectiveness and cost. Some things can be very efficacious but have such preposterous costs that they are not very efficient.

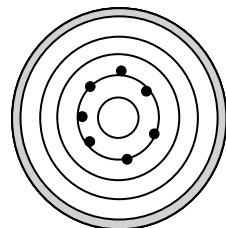
It is said that “Measurement theory is the art of feeling confident about being in error” (Chatburn 1996). A great deal of the technology related to mechanical ventilation of infants and children involves devices designed to measure various aspects of the interface between the ventilator and the patient. The clinician must be able to understand the strengths, limitation, accuracy, and

³This point continues to be debated by some who suggest that very small tidal volumes can be accurately measured with flow sensors that are back “inside” the ventilator, at the gas outlet and inlet with sensors that are reportedly accurate enough to measure from 5 to 1,000 mL. I believe this point has been largely discredited, but it continues to have its adherents. There will be more on this later in the chapter.

High precision low accuracy



High accuracy low precision



High precision high accuracy

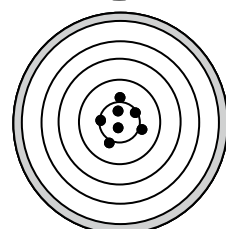


Fig. 67.2 Visual representations of various combinations of accuracy and precision

precision of these measurements to make an informed decision about whether you want to acquire this technology. Consider that *all measurements are erroneous*. This is why the terms *accuracy* and *precision* are important terms to fully understand.⁴ *Accuracy* is the agreement of a measured quantity to its actual or true value. *Precision* is the degree to which further measurements will display the same or similar results (also called reproducibility). A measure may be precise but not accurate, accurate but not precise, both, or neither. A measurement is considered valid if it is both “acceptably” accurate and precise. Figure 67.2 shows a visual representation of these terms.⁵

⁴The way that accuracy and precision are reported is somewhat confusing. To describe the accuracy of a flow sensor as 5 % (which is typical) is somewhat misleading, since it really describes the “inaccuracy” of the measurement. It could be said that the sensor is 95 % accurate. But until manufacturers and government regulators reconsider this more carefully, this reporting is not likely to change.

⁵Those interested in a deeper understanding of metrology as it relates to the testing and performance of medical devices are directed to the writings of my mentor and colleague Rob Chatburn (1996).

But what is “acceptable”? In terms of evaluating technology, how confident can you be that these errors are within a range of tolerance that still allows you to act upon these measurements clinically? It might be possible to produce a blood pressure cuff that can measure blood pressure with an accuracy of 0.005 mmHg, but who cares? Who is going to make treatment decisions on differences in blood pressure changes of this magnitude? If you are evaluating two devices that measure airway pressure and one is accurate to within 1.0 cmH₂O and the other is accurate and to within 0.10 cmH₂O, should you go ahead and pay for the additional accuracy and precision? Because you *will* have to pay for this added accuracy.

Note that accuracy and precision statistics listed by manufacturers are determined under ideal and controlled conditions *by the manufacturers*. As soon as you start putting mechanical ventilators on patients, you will find that these “ideal” figures for accuracy and precision sometimes cannot be duplicated.

Another often overlooked concept reminds us that the introduction of new technology can offer a benefit to our patients but also introduces *new risks* to patients. Sometimes new technology increases complexity in the clinical environment, which increases the chance for misapplication and mishap. Certainly the latest generation of mechanical ventilators adds a lot more weapons to the clinical armamentarium, but this complexity comes with a cost. It will take time for the clinical staff to really master the new devices. In the interim, patients are at increased risk of operator errors. If the design of the device is complex enough, this risk may not go away when the staff has “completed training.” There is no doubt that the more often clinicians do complex procedures and interventions, the better they become at it (Halm et al. 2002). But some of our most challenging devices, such as high-frequency oscillatory ventilators, are used infrequently enough to make me concerned about the maintenance of operating skills of the clinicians using these devices. I have observed serious misapplications of the oscillators that were caused by clinicians not using the ventilators often enough to maintain skills (or not understanding the basic physics and physiology of high-frequency ventilation).

Sometimes this increased risk to patients is worth it. Extracorporeal membrane oxygenation is incredibly risky but also offers the patients an incalculable benefit: life over death. So clinicians and families are willing to risk it. In the great calculus of risk-benefit analysis, this is the equation that must be solved. You must assess the potential benefit you are offering the patients and weigh it in the cosmic balance against the potential risk you are also introducing. This is particularly true when evaluating features the increasingly complex variety of features and modes available on the latest generation of mechanical ventilators.

67.2 Designing Your Own Ventilator Evaluation

When considering the purchase of mechanical ventilators, much detailed planning ought to proceed actually having the new ventilator in the hospital for bench testing or clinical trials. The concepts I am listing below I have developed over the span 20 years of testing and purchasing ventilators. I have led teams that did careful (and not so careful) evaluations of ten different models of mechanical ventilators, conducted a number of clinical trials, and then finally made purchasing decisions of over 85 mechanical ventilators of various types. Over this period I have developed a basic process for technology evaluation:

1. Why purchase new technology?
2. Which features are important?
3. Creating an evaluation team and a plan
4. Bench testing
5. Clinical trial
6. The decision

67.2.1 Why Purchase New Ventilators?

The quality of the evaluation and selection of new ventilators often falls apart before it ever really gets started. You should think very carefully about why you are considering new technology. In the case of ventilators, do not allow yourself to be the victim of slick marketing and ventilator envy. As stated earlier, ventilators are

marketed, just like automobiles, lawn mowers, and sneakers. All these products have something in common. They have a basic function, which, for the most part, all of them performs with adequate utility. Any car will get you down to the convenience store to buy a gallon of milk. Any lawn mower will trim your estate, and pretty much any sneakers will allow you drive the lane and toss up a jump shot. So to get you to buy a particular car, lawn mower, or pair of sneakers, marketers either create an image of their products that make you feel special when you use it, or they festoon their products with “features.”

I remember a manufacturer who ran a magazine advertisement for their somewhat overpriced and overengineered ventilator in the 1980s that was all about image and a bit short on evidence to back up their claims. The ad showed a picture of the ventilator, next to which there was an artist rendition of two terminal respiratory units. One unit looked healthy and normal, and the other unit was exploding outward, as if ruptured by overexpansion. It was a beautiful drawing and overall the ad was gorgeous. The ad was intended to make you think that if you purchased this ventilator, you would most certainly avoid overexpanding your patient’s alveoli and would have less ventilator-induced lung injury. This was predicated on their new feature, pressure-regulated volume control, which could allegedly deliver the same tidal volume with less airway pressure and thereby reduce the potential for lung injury. At the time of the ad, the academic critical care community was experiencing a growing awareness of the now widely held truth: that ventilator-induced lung injury (at least the mechanical type) is caused by volumetric overdistention of the lung. Thus, if a mode of ventilation gave the same volume using lower proximal airway pressure, there was no real reduction in the risk of lung injury. But their marketing sure was convincing.

I am unaware of any evidence base that supports the idea that any one mode of ventilation has any better effect on outcomes than any other. As I have said before, this is also true of all the different modes available on ventilators then and now. Alveoli can be damaged with any mode or brand of ventilator if improperly operated.

However, there are important differences in the ability of various ventilator brands to accurately measure gas flow at the interface between the patient and the ventilator in neonatal and pediatric applications. We now know that keeping tidal volume within a certain range improves outcomes from certain diseases. Thus, how accurately ventilators measure tidal pressure and flow and volume is an important performance issue, and I would recommend that when you are considering buying a neonatal or pediatric ventilator, you carefully assess the performance differences between ventilators in this important area.

So, the very first thing to do in any technology assessment with an eye towards purchase is to question the assumptions about why you need to buy the new technology in the first place. *All assumptions are suspect until proven otherwise.* The Toyota production system, one of the most effective and efficient methods of analyzing business processes teaches managers analyzing a complex issue/problem to ask why at least five times.⁶ Let’s try it: I need new ventilators:

1. Why? Because my current fleet of ventilators are old.
2. Why does this matter? Because I don’t have the latest technology.
3. Why does this matter? Because new technology is better.
4. Why is it better? Because newer technology is better for patients.
5. Why do you believe this is true?

Many arguments start to fall apart when drilled down to this level. Before you set out to evaluate technology, make sure your assumptions about why you want new technology are valid and are based on solid evidence. The field of respiratory and pulmonary care has a very uneven record of

⁶From Liker and Meier (2006). Some clinicians are understandably skeptical about the translation of learning from automobile production systems to clinical care systems. But our experience at Seattle Children’s Hospital and Research Institute has taught us that much can be learned from the Toyota Production System. At the time of writing, our hospital is publishing a textbook on health-care application of the continuous process improvement techniques learned from the Toyota system.

unproven and untested technology (Salzer 2008). Like any complex, organized human activity, many of our problems with poorly performing systems in health care are related to badly designed processes, over which we try superimpose technology in the hope that it will help improve things. Instead, what you usually end up with is a highly advanced, computerized, electronic, sophisticated process that remains highly dysfunctional.

Most of our technology will last much longer than the customary depreciation period now attached to most medical devices (5–7 years). This is clearly true since most of our “old” equipment is like our “old” military hardware. Once we don’t want to use it anymore, it is often resold to less developed countries and remains in use for many more years after we have discarded it.

It is more likely that you are considering buying new ventilators because of newly marketed “features.” Most of the growth in “features” in the last 30 years hasn’t borne much fruit with regard to improving outcomes. The last two wholesale ventilator replacements that I have promoted and executed were in search of improved measurement performance, not a search for allegedly advanced “features.”

67.2.2 Which Features Are Important?

There are a wide variety of decision drivers that inform the selection of a mechanical ventilator for infants and children. This will be to some extent specific to local intensive care environment. As an example, in some hospital designs there may be an economy of scale and efficiency to be gained by having a single ventilator that can be used in all intensive care units.⁷ The benefits of a single device include:

- Less training costs: fewer hours will be spent training all the clinical staff on various ventilators if you have a single machine that would work on all size patients.
- Improved staff proficiency: the clinical staff will get more experience with that specific single ventilator than if their clinical times were spread out over the operation of multiple types of mechanical ventilators.
- Reduced inventory costs: only one product line of supplies and parts will need to be maintained for a single ventilator.
- More efficient ventilator fleet utilization: since all ventilators could be used everywhere, it would be easier to move the ventilator fleet around to meet demand. There would be no possibility that one type of ventilator would be more utilized than the other and thus less likelihood that some types of ventilators would be sitting around unused. This would result in the overall need for fewer ventilators.

Of course, these advantages are based on the assumption that a single type of ventilator could ventilate all size patients in a neonatal and pediatric environment, from low birth weight babies to large adolescents. The ventilator industry has been in search of this technology for some time. Opinions vary about whether this has yet been achieved.

Listed below is a sample of a set of decision drivers and their relative weight in evaluating ventilators. In this example, the particular weights are not as important as is remembering that a carefully structured and methodical approach to this decision is essential. A careful planning process in your own hospital environment might result in different weights, depending on the factors specific to your hospital. For example, if a hospital had a very skilled and appropriately sized clinical engineering department, it might be possible for you to have all maintenance and repairs of the ventilator fleet done “in-house,” and thus, expenditures for outside maintenance could be less. In such circumstances ongoing maintenance costs might not have as high a weighting factor. Another example is a hospital with a large number of clinicians operating the ventilator with relatively low frequency, then the complexity of the user interface

⁷Some wags have dubbed this the “cradle to grave” mechanical ventilator. This might not be the best possible choice of words, since it is possible to go from cradle to the grave a little too quickly when mechanical ventilators are misapplied or misunderstood.

might be more heavily weighted as a decision driver. So the most important consideration is the specific population to be ventilated and the current local clinical culture about the best way to ventilate infants and children:

Factor	Weighting (%)
Physical design and available feature	15
Performance (measurement accuracy)	35
User interface design	20
Maintenance	20
Financial analysis	10

67.2.2.1 Physical Design and Available Features

67.2.2.1.1 Footprint/Appearance

The footprint is the square feet of floor space occupied by the ventilator. The appearance is its relative size and visual complexity.⁸ This is important because of the increasing number of devices now at the neonatal and pediatric critical bedside. I have seen episodes of care where the wrong device was inadvertently unplugged at the bedside of a critical patient. Visually, the room was a complex unorganized array of devices, hoses, tubing, cords, stands, monitors etc. Obviously this kind of complexity can lead serious clinical mishaps. Also, storage of ventilators when not in use is an important consideration in hospitals where storage space is constrained.

67.2.2.1.2 Mobility

The ease of movement of the ventilator will matter considerably to those charged with moving them around. This includes the likelihood of tipping over while moving. I once had an equipment technician who tipped over a brand new mechanical ventilator on the first day the device was uncrated. She was trying to move two ventilators at a time. If equipped with batteries, compressors, and cylinders, it is possible to transport patients around the hospital while attached to their ventilator (Jacques et al. 2005).

⁸I once stood in the doorway of a critically ill child and counted 22 display screens of various types at the immediate besides including cardiorespiratory monitors, infusion pumps, mechanical ventilators, ECMO pumps, and many more.

67.2.2.1.3 Battery Capability

Potential buyers should test the actual battery performance (as opposed to believing the stated performance data from the manufacturer). We have learned that batteries rarely perform as well as manufacturers claim. Also remember that battery performance deteriorates as the batteries age. So periodic retesting of battery performance is also recommended. Battery capability might be very important in hospitals with older utilities infrastructure where unplanned loss of electricity is more likely.

67.2.2.1.4 Compressors

Most modern ventilators can be equipped with a built-in compressor that allows the ventilator to operate without an external supply of compressed air. This can be important in care environments where there is a chance of an unplanned loss of compressed air to the ventilator, such as buildings with older utilities infrastructure or hospitals undergoing remodeling because of the chance of accidental cutting of existing gas lines during demolition. Adding these compressors will add cost and weight. My view is that this feature is well worth the additional cost and weight, particularly in pediatric and neonatal environments where the patients typically have less reserve to tolerate physiologic insults than adults.

67.2.2.1.5 Computer Interface

This refers to the ability of the ventilator to connect with the hospitals’ electronic monitoring and/or medical records systems. Almost all critical care ventilators now sold are equipped with serial RS-232 output connection (and other types) that can then be interfaced with the hospital systems or laptop computers. However, interface protocols may have compatibility issues with existing hospital systems, and work must be done to ensure compatibility before purchase. Also, some ventilators now have the capability to download stored patient-level ventilator measurements and settings onto removable media or laptop computers. This feature can be very useful, especially in retrospective analysis of troubling episodes of care. Additionally, some ventilators can download pulmonary graphic waveforms.

We have found this feature very useful, especially in analyzing questionable ventilator performance or patient-ventilator dyssynchrony.⁹

67.2.2.2 Modes

It is beyond the scope of this chapter to elaborate on the utility or relative merits of the large number of modes now available on most state-of-the-art critical care ventilators. As the availability of different control, triggering, and cycling variables has increased, it has created increasingly complex and unproven combinations of these control mechanisms using dual-control (blended) modes. Also adding to the confusion is the proclivity of manufacturers to create brand-specific names for modal features that vary from manufacturer to manufacturer. The interested reader is directed to the work of Chatburn and Primiano (Chatburn and Primiano 2001a; Primiano and Chatburn 2006) to better understand a standardized nomenclature of respiratory therapy and mechanical ventilation.

67.2.2.2.1 Control Variables

These may be either a pressure-controlled, or a volume-controlled, or a dual-control mode. Dual-control modes allow for a setting-targeted tidal volume combined with a decelerating flow wave form typically seen with pressure-controlled breaths. In this mode, the peak airway pressure is allowed to vary within certain limits to obtain the desired tidal volume. Opinions are divergent and in my view the evidence base is inconclusive about the relative merits of volume- versus pressure-limiting and decelerating versus constant flow modes, as well as dual-control modes of ventilation (Abubakar and Keszler 2005; Campbell and Davis 2002; Cheema and Ahluwalia 2001; Chiumello et al. 2002; Clark et al. 2000; Claure and Bancalari 2008;

D'Angio et al. 2005; Dembinski et al. 2004; Herrera et al. 2002; Keszler and Abubakar 2004; Kocis et al. 2001; Lista et al. 2004; Marraro 2003; McCallion et al. 2005; Piotrowski et al. 1997; Roth et al. 2004; Yang and Huang 2007). The interested reader is directed to the excellent review of this complex topic in neonates by (Keszler 2009).

In general, the conventional wisdom about the benefits of volume-targeted decelerating flow modes is thought to include (1) improved distribution of ventilation, (2) improved patient comfort and thus possibly less sedation required, (3) decreased patient-ventilator dyssynchrony, and (4) lower airway pressures (for the same tidal volume). The value of lowering airway pressure in neonates has been misconstrued and misrepresented over the years. It is clear to me that the risk of mechanical injury of the diseased lung is most closely related to *volumetric overdistention of the lung* (Brunherotti et al. 2003; Dreyfuss et al. 1988). This can occur at various pressures depending on the patient's respiratory system compliance. Thus, it is perplexing to me that there is a perceived benefit of lowering airway pressures while giving the same tidal volume. In neonates, volume-targeted decelerating flow mode is thought to be a better form of protective lung strategy because of the possibility of rapidly changing lung compliance and airway resistance in infants. But this would depend greatly on how nimble the ventilator is at adjusting the flow and pressure and the airway in response to changes in the patient's compliance and resistance (more on this later).

Some ventilators measure tidal volume at the proximal airway, and some measure tidal volume at the gas outlet from the ventilator. See the section on tidal volume accuracy below to better understand some of the issues with the location of these measurements.

There is also a debate about the relative merits of using inhaled versus exhaled tidal volume for the feedback to ventilator to run the volume-targeted modes. The relative merits of inhaled versus exhaled tidal volume measurement may seem an arcane subject, but the debate becomes more important when considering the airway

⁹Technically, the word "dyssynchrony" does not appear in the dictionary. The more commonly used word is asynchrony which means the absence of synchronization. But frequently, synchronization between the patient and ventilator is not completely absent, but is intermittently present, causing the patient-ventilator system to intermittently dysfunction. Thus, I prefer to use the admittedly made-up term "dyssynchrony."

leaks associated with the use of dual-control mode ventilation of infants and children with uncuffed endotracheal tubes. Leaks can make it more difficult for the ventilator to measure and control the true tidal volume. Some ventilator brands use exhaled tidal volume measurements to inform their dual-control systems, and others use inhaled tidal volume. Consider that some ventilators can measure and display both inhaled and exhaled tidal volumes and use these measures to represent a leak percentage:

$$\% \text{Leak} = \frac{VT_i - VT_e}{VT_e} \times 100$$

where

VT_i = inhaled tidal volume

VT_e = exhaled tidal volume

It is important not to forget that the ventilator displays are often customizable and that the tidal volume being displayed on the ventilator screen may not be the one that the ventilator is using for controlling the dual-controlled modes on the device. It may be that in the presence of a leak, some of inhaled tidal volume enters the trachea and immediately exits the trachea by leaking around the endotracheal tube during the inspiratory time and thus does not actually affect expansion of the lungs. In theory, using inhaled tidal volume measurements for feedback control helps to ensure that the actual tidal volume is no larger than that measured and controlled by the ventilator, but it is possible that the effective tidal volume might be considerably less, because of leakage around the endotracheal tube. When using exhaled tidal volume measurements, some of the tidal volume in the lung may leak around the endotracheal tube during the expiratory time, rendering this measurement lower than the actual tidal volume or the measured inhaled tidal volume.

67.2.2.2.2 Breath Averaging Versus Intra-breath Feedback

In dual-control modes, the ventilator has to adjust the flow and the allowable pressure to meet the volume targets for each breath. Some brands do this by using a running average of the activities of the last few breaths to set allowable limits for the

next breath. Others actually measure conditions during the current breath and adjust flow and pressure to attempt to meet the tidal volume target. One of the risks of dual-control modes is the phenomenon of overshoot. Consider the ventilators that use a running average to determine the limits of flow and pressure needed to give the targeted tidal volume. If the patient has been agitated and “fighting” the ventilator for several breaths (reducing lung compliance), some brands will increase the allowable pressure to try to give the targeted tidal volume in the next breath. But if the patient then suddenly relaxes, the pulmonary compliance can suddenly improve, and this increased pressure can then result in too large a tidal volume. This is theoretically less likely in ventilators that do adjustments of flow and pressure within a single breath. There has been very little published testing comparing these two approaches.

67.2.2.2.3 Triggering and Cycling Variables

In most currently available fifth generation critical care ventilators, breaths may be triggered (or started) and cycled (or ended) by either time or flow or pressure changes measured in the respiratory system. Essentially all critical care ventilators now offer various combinations of these variables in dual-control and pressure support mode configurations. The best combination of triggering or cycling variables to use on infants and children on ventilators is still not completely understood although there is a growing body of research in this area (Greenough et al. 2008). As practice evolves the use of flow triggering and cycling is increasing. Some brands of ventilators have adjustable flow cycling thresholds, while others have a preset level. See the section on work of breathing and patient-ventilator dyssynchrony. Other triggering methods have been tried over the years including triggering off of changes in thoracic impedance, abdominal wall movement, and diaphragmatic innervations (Kondili et al. 2009). None of these has been widely adopted. Neurally adjusted ventilatory assist uses the measurement of diaphragmatic activity to trigger the ventilator. It shows some promise

(Bengtsson and Edberg 2010; Breatnach et al. 2010; Spahija et al. 2010) but much research needs to be done before the benefits of this technology can be established. This requires the insertion of a specially equipped gastric tube orally or nasally. It seems premature to consider this feature a major decision driver in the selection of a neonatal or pediatric ventilator.

67.2.2.2.4 Airway Pressure Release Ventilation (APRV)

This relatively recent addition to modes available on some ventilators remains largely untested in neonates and pediatric patients. Fundamentally this mode resembles pressure-controlled inverse ratio ventilation but is different in that it allows for spontaneous breathing on top of relatively high continuous airway pressure during prolonged inspiratory phase of the respiratory cycle. Whether or not this is an essential feature of mechanical ventilators for infants and children is unknown. The relatively small amount of published literature about APRV is divergent with some reports suggesting a salutary effect on patients (Habashi 2005; Kamath et al. 2010; Krishnan and Morrison 2007) and others finding no benefit (González et al. 2010). My own view is that it requires considerable additional training in ventilator management for physicians, nurses, and respiratory therapists, since the ventilator variables that affect oxygenation and minute ventilation are significantly altered in this mode. There is insufficient evidence at this time to support the inclusion of APRV in available modes as a major decision driver in selecting neonatal and pediatric ventilators.

67.2.2.3 Other Features/Issues to Consider

67.2.2.3.1 Leak Compensation

It is reported that 70 % of intubated neonates have an airway leak >10 % (Bernstein et al. 1995). Many ventilators now have sophisticated algorithms for rapid adjustment of flow profiles in the patient-ventilator system to compensate for airway leaks, and there appear to be differences in performance of these leak compensation protocols between brands of ventilators

(Mehta et al. 2001). Without leak compensation, ventilators that flow trigger are prone to excessive autocycling. In my experience these algorithms are important when assessing ventilator performance because there tend to be more and larger leaks in the neonatal-pediatric population because of the use of uncuffed endotracheal tubes. Bench testing of ventilator performance should include tests with and without the leak compensation activated and include the presence of a constant but adjustable leak. This is possible in some sophisticated lung models.

67.2.2.3.2 Response Time

There is little consensus around a precise definition of response time, but it is usually described as the elapsed time (in milliseconds) from when the proximal airway flow (or pressure) changes enough to activate the trigger threshold until the time when sufficient flow has been added to the system to bring the flow (or pressure) signal back to baseline. Relatively short response times are necessary to improve patient-ventilator synchrony. There are clearly differences in response time between brands of ventilators, but there is also a lack of agreement on the exact definitions of response time (Ferreira et al. 2008; Heulitt et al. 2000; Salyer et al. 1992; Terado et al. 2008). Breaths may be triggered by changes in flow or pressure, movement of the abdominal wall, changes in thoracic impedance, or diaphragmatic electrical activity. The most widely used triggering variable for spontaneous breaths is flow. The conventional wisdom now holds that flow triggering is the best method of synchronized triggering, but little testing in humans has never been done to verify this assumption (Donn and Becker 2003). Testing of response time between devices being evaluated is recommended, and all other things being equal, ventilators should be selected with the shortest response time possible.

67.2.2.4 Alarms

67.2.2.4.1 Overall Volume and Distinctiveness

The growth in the number of monitoring devices and alarms in the critical care environment has made it increasingly challenging to discern

and differentiate unimportant or false alarms from meaningful alarms (Chambrin et al. 1999; Gorges et al. 2009; Lawless 1994; Sabar and Zmora 1997). Thus, a common design for ventilator alarm packages has two levels of alarms, a lower level for alarms that are not necessarily life threatening and an upper level for critical alarms that require an immediate response/intervention. This is essential since a large proportion of alarms in the critical care environment are low priority or “nuisance” alarms. The alarm volume should be adjustable from low volume to high volume, so that the alarm level can be customized to the care environment. In neonatal units, lower volumes might be advisable to minimize noxious stimulation of the patient.

67.2.2.4.2 Remote Alarm

The design of some intensive care units provides for the connection of ventilators and monitors to a system that creates audible and/or visible alarms outside the patient rooms. This decreases (but does not eliminate) the likelihood that critical alarms can go unnoticed if no one is in the patient’s room. This is an essential feature, particularly for monitoring the ventilation of infants and children. Their inability to cooperate creates an increased likelihood of accidental disconnection from the ventilator, and their small size increases the likelihood of accidental extubation. Plus, rapid response to alarms is particularly important in this population because of increased sensitivity to physiologic insult.

67.2.2.4.3 Essential Parameters to Monitor with Alarms

Many ventilators now have a vast array of alarm capabilities. For the purposes of patient safety, the essential alarms for neonates and children include:

- Circuit disconnect
- High and low peak airway pressure
- High and low positive end-expiratory pressure
- High and low minute ventilation
- High and low FiO_2
- Low source gas pressures

Accidental disconnection of the ventilator circuit is the most common threat of mishap with a mechanical ventilator. Some ventilators now have sophisticated algorithms for detection of disconnection that have rendered the alarms very sensitive and specific. However, testing of disconnection alarms under various conditions is advisable.

67.2.2.5 Performance

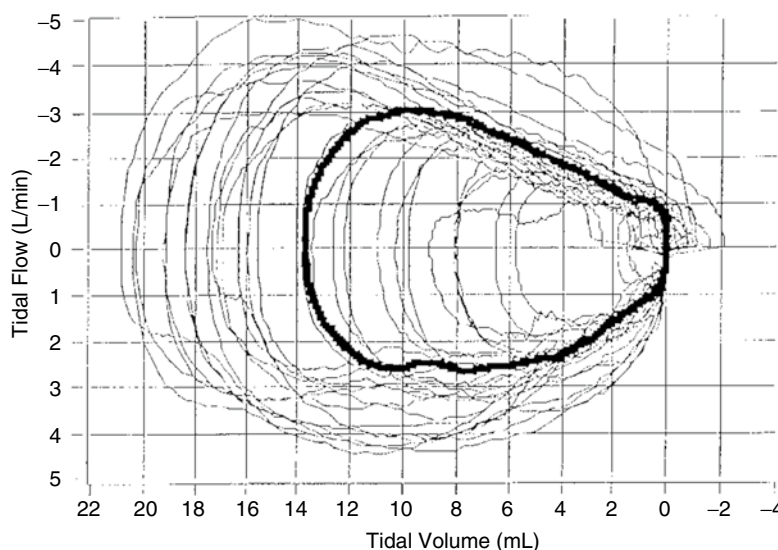
67.2.2.5.1 Tidal Volume Accuracy

A significant challenge in ventilating infants and small children is the accuracy of tidal volume measurements. Many ventilators currently being used in infants and children were not specifically designed for use in this population. As such the precision and accuracy of their tidal volume measures are acceptable for the ranges of flows and volumes used in adults, but may not be sufficiently accurate for the measurement of very small tidal volumes in infants and children. As an example, one widely used ventilator in both adults and pediatric populations has a stated tidal volume accuracy of $\pm 1 \text{ mL} + 10 \%$ of reading. So if the tidal volume measurement on the ventilator is reading 20 mL, the actual tidal volume could be between 17 and 23 mL, which in reality is $\pm 15 \%$, and still be within the stated accuracy of the instrument. This is right at the limits of what I would consider acceptable since careful control and limitation of tidal volumes is so important in preventing ventilator-induced lung injury. But if the tidal volume is reading 4 mL, the actual tidal volume could be between 2.6 and 5.4 mL, which is actually $\pm 35 \%$. The use of very small tidal volumes (4–6 mL/kg) in very low birth weight infants (<750 g) is increasing, and as this happens, some ventilators are challenged to accurately deliver and display tidal volumes.

67.2.2.5.2 Location of Tidal Volume Measurements

The large volume of gas in a ventilator circuit, relative to the very small tidal volumes being delivered to neonates and small children, makes measurement of tidal volume at the proximal airway seem the best configuration for accurate determinations. This has been repeatedly

Fig. 67.3 Tidal breathing flow-volume loops derived from measurements of a healthy preterm infant with estimated gestational age at birth of 29 weeks and birth weight of 1,300 g. Note the high breath to breath variability (Used with permission from Paetow et al. (1999))



verified by my clinical observations. The preponderance of the literature supports this notion. It has been repeatedly reported that very small tidal volumes cannot be accurately measured with sensors that are back inside the ventilator, but instead, a proximal flow sensor is required (Cannon et al. 2000; Castle et al. 2002; DiBlasi et al. 2007; Neve et al. 2003; Salyer and Jackson 2005a; Chow et al. 2002; Roske et al. 1998). A single research lab has suggested that this is not necessarily true with one particular brand of ventilator (Heulitt et al. 2005, 2009), but their findings have not been duplicated by others. Thus, I recommend that any ventilator to be used on neonatal or small pediatric patients has the capacity to measure tidal volume at the proximal airway.

There are currently two proximal airway volume measurement technologies that are available on various ventilators: (1) disposable differential pressure pneumotachometer and (2) reusable heated wire anemometers. Under ideal conditions these sensors have similar accuracies, in the range of +10 %. However, in practice these two types of sensors have strengths and weaknesses. The heated wire sensors are prone to the accumulation of moisture from condensation of the heated humidified gas passing through them. It is necessary to periodically remove the water from the sensor and to occasionally change the sensor because of degraded performance related to the condensation. The disposable pneumotachometers

are also prone to problems with accumulated water, in this case inside the pressure sensing lines that go back to the ventilator. This problem was serious enough that we stopped using them and went to the heated wire anemometer for all neonatal patients (the brand of ventilator we were using had the capacity to use either style of proximal flow sensor).

67.2.2.5.3 V_T Variation in V_T -Targeted Decelerating Flow Mode

As stated above, tidal volume targeting is accomplished using different approaches to control algorithms depending on ventilator brand. Consider that spontaneous tidal volumes are highly variable in newborns. Paetow et al. showed that spontaneous tidal volumes were highly variable in both healthy infants and those with significant lung disease (Paetow et al. 1999). Within the same patient spontaneous tidal volumes ranged from 2.0 to 22 mL (Fig. 67.3). This high variability has implications for the ventilators that attempt to do volume-targeted decelerating flow-type (dual control) modes since the ventilators must rapidly change their flow profiles and pressure limits to try to adjust the targeted tidal volume in the face of this high variability.

One widely sold ventilator has a volume limitation feature such that in volume-targeted modes, a maximum allowable V_T for each breath can be set. This, combined with a volume target, creates

a “bracketed” tidal volume range. In theory this ought to help minimize the risk of volumetric overdistention of the lung, but there is very little published testing about this.

Thus, the ability of the ventilator to maintain targeted tidal volumes within a specific range should be tested. We developed a bench test to analyze this capability in ventilators. See the section on bench testing.

67.2.2.5.4 Work of Breathing and Patient-Ventilator Dyssynchrony

The interface between the ventilator and the patient is the point where the performance of neonatal and pediatric ventilators is sometimes challenged. Poor response to the patients’ own respiratory cycle can lead to dyssynchrony and an increase in the imposed work of breathing. There are reported differences in the imposed work of breathing among certain ventilators (el-Khatib et al. 1994). It is thought that imposed work of breathing was related to trigger design and that flow triggering reduced the imposed work of breathing and/or patient-ventilator dyssynchrony (Branson et al. 1994; Dimitriou et al. 1998; Sassoon et al. 1994; Stayer et al. 2001; Uchiyama et al. 1995). The responsiveness of the ventilator to infant breathing patterns can be tested, and I discuss this in the section on bench testing.

67.2.2.6 User Interface

67.2.2.6.1 Ease of Training/Use

The introduction of new ventilator technology introduces risk to the patient since there will be a period of transition when the clinical staff will need to be trained and *become proficient at operating these new devices*. During this period there is real risk to patients of operator-induced application errors. I have seen this repeatedly. We often commit insufficient resources and attention to training. The amount of training time required for new ventilators will be difficult to estimate, but when evaluating new products, the complexity of the interface and resultant training burden should be considered.

67.2.2.6.2 Simplicity

The interface between ventilator and operator should be kept as simple as possible. The advent

of computerized ventilator control screens has led to the introduction of hierarchical user interfaces. This requires users to learn (sometimes) fairly complex pathways to “drill down” to all the control and configuration screens. I have learned that the more screens and more complexity there are in the interface, the greater the likelihood for the operators to overlook important setup and configuration issues like pre-use operational verification procedures and system leak tests. The interface design can have an important impact on the quality of care, although our efforts to quantify this are nascent (Fairbanks and Caplan 2004; Gonzalez-Bermejo et al. 2006). Uzawa and colleagues executed an interesting study of user interfaces in modern critical care ventilators, which the interested student could use as a framework to craft their own interface evaluation (Uzawa et al. 2008).

67.2.2.7 Financial Analysis

67.2.2.7.1 Purchasing Costs

The seemingly high initial capital cost of acquiring modern mechanical ventilators is actually less important than the ongoing operational cost. One way to think of this is to consider how many days a typical ventilator will be in use during its operational life. If a ventilator has a useful life of 7 years (which is on the low end of the scale) and is in use about 75 % of days (fairly high utilization), then the acquisition costs spread out over all days of use are actually comparatively low. Assuming an acquisition cost of \$30,000 (US) and the total days of use was $7 \times 365 \times 0.75 = 1,916$ days, the cost per applied ventilator day was $\$30,000 \div 1,916 = \$15.65$ per day. This is typically called the depreciated capital acquisition cost. Daily supply and labor costs to operate the ventilator will typically be higher than the acquisition costs. Special care must be taken to appreciate all the costs that will be attached to the use of the ventilator when evaluating a device for purchase:

67.2.2.7.2 Operating Costs

These costs include ventilator circuitry, filters, exhalation valve assemblies, humidification supplies, and labor. A complete thorough assessment of the daily costs of all of these supplies is an

important of the financial analysis of a ventilator purchase. Ventilators with more complex setup, calibration, and assembly may require more labor costs. Pay attention to costs of disposable exhalation valve assemblies, cleaning costs of reusable assemblies, disposable flow sensors and the cleaning costs of reusable sensors, and oxygen analyzer fuel cells and any calibration kits that might be required.

67.2.2.7.3 Maintenance Costs

There can be considerable differences in ongoing maintenance costs between brands of ventilators. These periodic expenses can include parts replacement, maintenance kits, training of clinical engineering staff, shipping costs for parts or ventilators, and labor hours of local clinical engineering staff. This can often be a negotiating point with manufacturers to help reduce operating costs by shifting some of these expenses to the manufacturers.

67.2.2.7.4 Upgradeability Cost (and Ease)

There is a high pace of technological advancement in the ventilator design and performance. As newer technologies have emerged and been distributed, feedback from users often leads companies to offer upgrades that address problems that have surfaced only after widespread clinical use. My colleagues executed a series of tests over time on a fleet of mechanical ventilators that eventually lead to improvements in ventilator performance (Crotwell et al. 2007). During a ventilator evaluation, thought should be given to assessing the ease with which ventilator operating software can be upgraded and the potential cost of future upgrades, most of which should be borne by the manufacturer.

67.2.3 Creating an Evaluation Team and Format

One of the worst things you can do when setting out to evaluate and possibly acquire new ventilator technology is to have the hubris to go it alone. You must first create team to manage and execute this complicated project. You should carefully consider

all the stakeholders.¹⁰ For mechanical ventilation this will typically include medicine, nursing, clinical (or biomedical) engineering, and respiratory therapy (in the parts of the world that employ respiratory therapists). For hospitals with multiple intensive care units, be sure to include physician representatives from each of the intensive care units. And in some health-care systems, you may want to include anesthesia, pulmonology, and surgery representatives too. They may not want to participate but it is much better to have asked them and had them decline than to have to explain later why they were never asked to participate. One way to think of this group is as a guidance team, which will help oversee the evaluation project.

Take some time to think about who the right players are for this team. I know of a respiratory therapy director in North America who did not include the neonatologists in the process of selecting new ventilators. This probably helped contribute to the selection of a ventilator that really wasn't very good for neonates. The director was understandably trying to standardize technology across the critical care continuum, from neonates to adults. But he did not do a sufficiently rigorous evaluation. When the new ventilator showed up in the NICU, it quickly became obvious that it wasn't suitable for neonates. The neonatologists soon banned the ventilator from the NICU, and before long the director was looking for employment elsewhere.

I know of another example where new ventilators were acquired as additions to the current fleet. Unfortunately, there did not appear to be much of a detailed evaluation done, and there was very little participation in the process from various clinical disciplines. I suspect they were purchased mostly because of (1) the reputation of the company, (2) the skill of the local ventilator manufacturing representative, and (3) the irresistible lure of new "features." Predictably, the ventilators sat around and did not get used by the staff.

¹⁰Stakeholders are those who have a stake in the system or process that you are considering changing. Stakeholders are very important parts of implementing change. If you have all (or most) of the stakeholders participating in your project, you will greatly advance its chances for success.

You should do some prep work before the first meeting of this team. Outline a rough plan for your evaluation. It is always better to come to a meeting with something for people to react to. It is very difficult to create plans from scratch in a meeting environment. Remember that one of the biggest problems with carefully executed, collaborative planning in hospitals today is getting everyone in the room at the same time. Scheduling meetings has become very difficult. Pay close attention to not wasting anyone's time and do as much work as can be done outside the framework of the meetings.

The "Six P Principle" says that proper planning prevents piss poor performance. It is really tragic how much managerial pain and suffering could be alleviated by careful and thorough planning.¹¹ But the converse is also true; for a project as complex as an evaluation for the purchase of a large fleet of mechanical ventilators, you must also be willing to adjust and modify your plans when conditions and assumptions change.

67.2.4 Bench Testing

Users of advanced ventilator technology ought to be willing to spend more time and energy than they typically do in testing the claims of the ventilator manufacturers. This is particularly true in neonatal and pediatric applications, since most new critical care ventilators are not really designed from the start specifically for use with infants and children. By bench testing devices you are considering purchasing, you learn a lot about how they work or more importantly you can identify some conditions where they don't necessarily work so well. The basic equipment you need for bench testing is simulators and measurement instruments. Simulators help you mimic clinical conditions, and measurement instruments help you verify the performance of

the devices you are testing. They range in complexity from test lungs like rigid bottles and containers, to simple bellows, to pistons, and all the way to very sophisticated, programmable breathing simulators. Here is a list of companies (and their websites) that make test lungs and breathing simulators:

- IngMar (www.ingmarmed.com)
- Michigan Instruments (www.michiganinstruments.com)
- South Pacific Biomedical (www.southpb.com)
- Hans Rudolph (www.rudolphkc.com)
- VacuMed (www.vacumed.com)
- Intermedical (www.intermedical.com)
- Si-Plan Electronics Research (www.si-plan.com)

Successful bench testing of mechanical ventilators requires the use of devices for the precise measurement of flow and pressure at the airway opening of the test lung. The most common of these devices are computerized pneumotachometers (O'Donnell and Webb 1998), of which there are many types and brands. Small, relatively inexpensive pneumotachometers are manufactured for use as ventilation monitors that are well suited for use in bench testing ventilator performance (Al-Majed et al. 2004; Sasaki et al. 2003; Tracy et al. 2004). Other measurement devices for equipping a bench testing lab include pressure manometers, flow meters, thermometers, barometers, and hygrometers.

Another simple and very reliable method for tidal volume testing is to use rigid test lungs with a known compliance. With such a lung analog, tidal volumes can be determined by multiplying the pressure developed at the opening of the lung by the compliance of the lung. For typical ventilator testing, the change in pressure should be used, i.e., the peak inspiratory pressure minus the positive end-expiratory pressure. As an example, when ventilating a rigid test lung, true or actual tidal volume can be determined by:

$$AV_T = (C_{TL}) \times (PIP - PEEP)$$

where

AV_T = actual tidal volume

C_{TL} = compliance of the test lung

¹¹Definition of planning: to bother about the best method of accomplishing an accidental result.... Ambrose Bierce (1842–1914). This is from the devil's dictionary at www.alcyone.com/max/lit/devils/.

Table 67.1 Results of a bench test of the accuracy of the displayed tidal volumes on the Servo 300 when ventilating a neonatal lung model designed to mimic a 1,000 g infant

Ventilator mode	V_T actual (CO ₂ SMO)	V_T displayed (Servo)	V_T displayed error (%) (Servo)	V_T corrected	V_T corrected error (%)
PC	9.9	35.1	255	1.7	−83
VC	11.2	35.0	213	−0.9	−108

PRVC pressure-regulated volume control, *TCPL* time-cycled pressure limited, *VC* volume control, *CO₂SMO* is a brand name of a computerized pneumotachometer.

PIP=peak inspiratory pressure
PEEP=positive end-expiratory pressure
If the PIP=25 cmH₂O, PEEP=5 cmH₂O, and $C_{TL}=0.3$ mL/cmH₂O, then actual tidal volume would be equal to 6.0 mL.

67.2.4.1 Bench Testing Case Study

What follows is a narrative of a series of bench tests we undertook to test the performance of mechanical ventilators for use in neonatal and pediatric patients. When I say “we,” I am referring to my respiratory therapy colleagues at Seattle Children’s Hospital and Research Institute.

One day a respiratory therapist came to me with copies of a ventilator flow sheet and a story. He was caring for a 900 g neonate on a Servo 300, the only neonatal ventilator used in our NICU at the time. According to the ventilator flow sheets, the corrected exhaled tidal volume was in the range of 6–8 mL/kg. Corrected tidal volume was determined by formula “a” in Table 67.2.

The clinicians had doubts about the veracity of these corrected tidal volume data, owing to their clinical observations of the patients’ chest rise and breath sounds. So they put a computerized pneumotachometer at the proximal airway to verify tidal volumes. The pneumotachometer indicated that the patient was getting a tidal volume in the 14–16 mL/kg range. We decided to test the accuracy of the tidal volumes displayed by a Servo 300 in a bench test model. We used a static neonatal lung model and a typical ventilator circuit. The lung was ventilated with a Servo 300 in two different modes, pressure control and volume control. Tidal volumes were determined for each breath in three ways: (1) the displayed tidal volume on the ventilator, (2) the corrected tidal volume as described above, and 3) the actual tidal volume as measured by a computerized pneumotachometer placed at the proximal

airway. We then calculated tidal volume errors according to formula “b” in data for 50 breaths that were gathered. Table 67.1 shows the results of our simple bench test of a single Servo 300 ventilator and is typical of the kinds of testing that can and should be done as part of an evaluation of a ventilator for purchase. We tested the ventilator in volume control and pressure control.

I want to stop and point out that we were testing the Servo 300 at the extreme lower end of its operating limits. This narrative is intended to point out the value of bench testing, not to question the reputation of the Servo ventilators in general, which are widely respected in the RT community. This test was narrowly focused on the accuracy of displayed tidal volumes in the neonatal range, something which the Servo 300 was not principally designed to do. Another limitation to bench testing is the testing of single device. Ideally, five or ten ventilators of each brand would be tested in order to have a higher degree of confidence that the performance of the ventilators tested could be inferred on the population of all ventilators of that particular brand and model. However, such large-scale testing is generally not feasible.

These findings led us to execute a series of bench tests to inform a purchase decision for a new fleet of ventilators. An outline of our methods is listed in Table 67.2. We set out to bench test the displayed tidal volume accuracy of a range of ventilators that were considered “neonatal” or “pediatric.” We surveyed the ventilator market and selected a group of ventilators to test that included six different brands. I have blinded the names to focus on the methods and process of bench testing. Actual V_T was determined independently of the ventilator display with a pneumotachometer placed at the proximal airway. The ventilators were set to operate

Table 67.2 Sample outline of bench testing protocol for tidal volume accuracy of neonatal-pediatric mechanical ventilators

1. Purpose
1.1. Determine the accuracy of displayed tidal volumes
2. Methods
2.1. All ventilators tested will be equipped with the latest software from the manufacturers
2.2. Exhaled tidal volume will be measured independently at the proximal airway with a differential pneumotachometer
2.3. All tidal volume measurements will be made on the same disposable, dual-heated wire, humidified ventilator circuit with proximal airway temperature set at 37 °C and the gradient between humidifier output temperature and proximal temperature set at −2.0 °C
2.4. Accuracy of the pneumotachometer will be verified before each run of data acquisition using a 5.0 mL Hans Rudolph calibration syringe. Readings must be within ± 10 % of 5 mL (4.5–5.5 mL)
2.5. Test lung used will be a rigid container with compliance of 0.4 mL/cm
2.6. Ventilator settings will be peak inspiratory pressure = 35 cmH ₂ O, positive end-expiratory pressure = 5 cmH ₂ O, frequency = 20/min
2.7. Exhaled tidal volumes displayed by the pneumotachometer and by the ventilator will be recorded for each breath
2.8. Runs will consist of at least 50 breaths for each device tested
2.9 For ventilators that do not have proximal airway sensors, corrected tidal volume for each breath will be calculated according to the following formula (a): $VT_C = VT_E - [(PIP - PEEP) \times C_T]$ where VT_C = corrected tidal volume VT_E = displayed exhaled tidal volume from the ventilator C_T = tubing compliance factor
2.10. Typical descriptive statistics will be calculated for tidal volumes displayed by the ventilator, displayed by the pneumotachometer, and corrected by formula (a) for devices without proximal flow sensors
2.11. Tidal volume error percentages will be determined by the following formula: (b) for each ventilator tested $\text{Tidal volume error (\%)} = \left[\frac{\overline{VT_D} - \overline{VT_A}}{\overline{VT_A}} \right] \times 100$ where : $\overline{VT_D}$ = mean displayed tidal volume $\overline{VT_A}$ = mean actual tidal volume

in volume-targeted decelerating flow modes and connected to a static neonatal test lung. Ventilators were set to deliver either 5 mL (low V_T) or 10 mL (high V_T) with the exception of model C which was tested only in the high V_T setting because 10 mL is the lowest volume setting on the device. Percent error was calculated according to formula (b) in Table 67.2.

We used exhaled tidal volumes for all measurements and computations. Table 67.3 lists the results of our testing. We found important differences in the displayed V_T accuracy of these neonatal ventilators. This bench research was an important part of our process of ventilator selection. Although our bench studies were intended to inform our decision to select a new

mechanical ventilator, we also published our results (Crotwell et al. 2007; DiBlasi et al. 2007; Salyer and Jackson 2005a).

Table 67.3 Results of a bench test of the accuracy of the displayed tidal volumes on the several “neonatal” ventilators

Ventilator	Overall error rate (%)	Low V_T error rate (%)	High V_T error rate (%)
Model A	10.1 ± 9.6	14.1 ± 11.7	6.2 ± 4.2
Model B	16.8 ± 4.4	19.3 ± 4.5	14.4 ± 2.6
Model C	−19.6 ± 0.9	N.A.	−19.6 ± 0.9
Model D	74.3 ± 127.1	47.9 ± 10.2	106.9 ± 185.9
Model E	20.5 ± 28.4	3.5 ± 29.9	37.2 ± 12.7

Data are represented as mean error rates ± standard deviation
 Error rates are calculated as (actual V_T − displayed V_T) / actual V_T

Table 67.4 Sample protocol for testing the variability of exhaled tidal volumes during neonatal volume-targeted decelerating flow modes

1. Purpose: Determine the variability in the ventilator’s ability to achieve targeted tidal volumes in the presence of erratic spontaneous breathing
2. Methods:
2.1 Test lung used is IngMar ASL 5000
2.2. Test lung settings used will mimic an erratically breathing infant, with periods of tachypnea, eupnea, and apnea, superimposed on periods of small and large spontaneous tidal volumes according to the following epochs (see Table 67.5)
3. This erratic breathing pattern is being programmed into the ASL and reproducible for all tests. Each instrument will be operated in volume-targeted decelerating flow mode for a minimum of 3 min
4. Tidal volume will be measured independently at the patient airway with a computerized pneumotachometer (Cosmo)
5. Coefficient of variation of delivered tidal volume will be calculated for each device
6. At the end of this cycle of testing, we would select the two best devices to test clinically. The best being defined as a combination of the most accurate tidal volume display and lowest coefficient of variation in delivered tidal volumes

We were also interested in evaluating a second aspect of ventilator performance in the neonatal range. Each ventilator had the capacity to deliver volume-targeted breaths with a decelerating flow profile. But we knew that each company had different computer algorithms that controlled the ventilators’ response to rapidly changing lung mechanics in spontaneously breathing infants. So we set out to model erratic spontaneous breathing in a neonate.

Tables 67.4 and 67.5 are details of our methods. We used the Ingmar Active Servo Lung 5000 (Ingmar Inc.) simulator to mimic neonatal breathing. The simulator allows programming of individual breaths or groups of breaths to create a reproducible erratic breathing pattern. The spontaneous breathing model was programmed for 196 s runs including epochs of apnea, eupnea, and tachypnea, with varying tidal volumes. Again the same pneumotachometer was used to independently measure exhaled V_T . Ventilators tested included the same six brands tested earlier. Each ventilator

Table 67.5 Programmed breathing epochs for the lung simulator (ASL 5000)

Duration (s)	Breathing frequency (per min)	T_I (s)	Insp Pmax (cmH ₂ O)	V_T (mL)
24	30	0.40	10	4.3
15	100	0.20	5	1.8
6	0	0.00	0	0.0
15	80	0.30	4	1.4
12	20	0.40	10	4.3
12	10	0.45	7	2.8
7.5	0	0.00	0	0.0
6	100	0.20	15	6.7
15	40	0.35	12	5.4
12	20	0.40	10	4.3
15	100	0.20	5	1.8
6	0	0.00	0	0.0
15	80	0.30	4	1.3
12	20	0.40	10	4.4
9	100	0.20	10	4.3
15	20	0.40	8	3.3

Total time of the simulation was 196.5 s. These settings were intended to mimic a high degree of erratic breathing. Insp Pmax is a setting on the breathing simulator that is analogous to the maximum inspiratory pressure that the piston will generate. V_T mean tidal volumes created by the test lung for each epoch as measured with an independent pneumotachometer, T_I inspiratory time

was set up with a typical circuit to give $V_T=5$ mL in their respective modes for volume-targeted ventilation, with decelerating flow.

Our assumption was that the best ventilator performance would result in the tightest distribution of tidal volumes. As the baby (lung simulator) breathed erratically, the ventilator would have to make rapid changes in the dynamics of flow in order to try to keep the tidal volumes in the targeted ranges. Figure 67.4 shows the distribution of tidal volumes for each ventilator tested, which we also published (Salyer and Jackson 2005b). There were clearly very important differences in the distribution of tidal volumes.

These data were very important in our decision making about which ventilators to select for a clinical trial. There were costs associated with these bench tests:

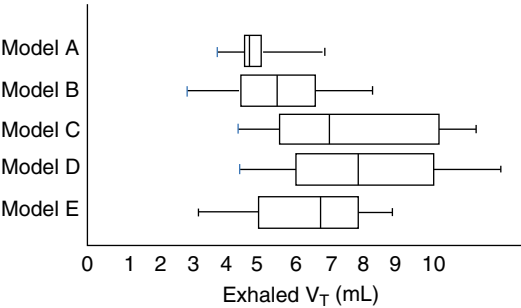


Fig. 67.4 Example of results of testing neonatal ventilators for delivered tidal volume variability during volume-targeted ventilation in a neonatal lung model of an erratically breathing infant

Breathing simulator leased for 3 months	\$1500 ¹²
Labor cost to pay my staff for training and bench time	\$2000
Other miscellaneous costs	\$1000

For a very large purchase (in our case about 30 mechanical ventilators at \$28,000 each or about \$850,000), an investment of about \$4500 seems very reasonable to help ensure that you have made the best decision possible.

At this point it is time to review about how we managed the manufacturers through this process. We included them at every step. We shared the testing protocols with them, offered them the chance to suggest changes to our protocol, and invited the local reps and anyone they wanted to bring along to come and be present for testing. However, there was an explicit agreement that testing was completely controlled by us, and the manufacturers were there in an advisory capacity only. This arrangement also helped us to set up and operate ventilators with which we were not very familiar.

Clinical engineering should play an important role in product testing. In fact, in some organizations, this kind of focused bench testing would be executed by the clinical engineering department. Early on, I met with the manager of clinical engineering, who reviewed all our designs and was invited to come and observe the testing.

¹²You can buy an IngMar ASL 5000 for around \$30,000.

Another excellent resource for those trying to evaluate medical equipment like mechanical ventilators is ECRI (www.ecri.org). The Emergency Care Research Institute has been called by the New York Times “the country’s most-respected laboratory for testing medical products.” They can be an invaluable resource for keeping abreast of the latest developments in technology assessments.

67.2.5 Clinical Trial

Based on the results of our bench testing and other considerations, we selected a product to test clinically. There was a time in this business when ventilator evaluations would go like this: a single ventilator would be brought in, and a handful of people would get some rudimentary training, usually for 20 min at the change of shift, often at the bedside. Then the ventilator would get put on a handful of patients over a period of a couple of weeks. There was little rigor with regard to a priori determinations of what would be successful endpoints of such a clinical trial. We were determined to avoid engaging in what Einstein described as insane behavior.¹³

As we began planning our clinical trials, my number one concern was patient safety. I knew that the introduction of new ventilator technology posed a real risk for patients, since it greatly increased our chances of operator error. We also knew that doing an extensive clinical trial would help to ensure that we would expose any design and performance flaws the devices had.

So we did a lot of careful planning related to when and how we would introduce the ventilators into clinical practice. Since we were going to live (or die) with this decision for many years, I wanted to ventilate enough patients of various kinds to get a good assessment of how well the ventilator would meet our patients’ clinical needs. Here are some important considerations we developed:

¹³Einstein defined insanity as, “doing the same thing over and over again and expecting different results.”

- No one would be allowed to operate the ventilator who had not been trained and demonstrated basic competency user return demonstrations. Here is what this really meant. Clinicians could not skip in-service training, show up for duty, and get trained by the clinician who was going off duty at the bedside at change of shift.
- Training was mandatory for all respiratory therapists working in critical care at the time. We decided to train everyone for the clinical trial since, presumably, everyone would be using the ventilators if we bought them, and we wanted lots of interaction and experience with the ventilators. This was a large commitment but we were determined to minimizing patient risk and conduct a thorough assessment. Thus, it took several weeks of training before we could even put a single ventilator on a patient.
- All training took place outside the clinical environment. By this I mean in controlled classroom environments where interruptions were minimized. Staff members were trained during hours when they were not actively taking patient assignments, e.g., after their shift (not good), before their shift (better), or on their days off.
- We selected a group of volunteer respiratory therapists to receive advanced training. They were designated as “experts and we selected and scheduled them in such a fashion that at least one was on duty at all times.
- We required a nearly constant on-site clinical presence from the manufacturer’s representatives during the trial. After negotiation they agreed to bring in a team that pretty much managed round the clock coverage. There were occasional uncovered periods in the wee hours, but the representatives stayed in nearby hotels and could be back in the hospital within a few minutes of being called.
- We did some careful planning with our medical staff about the kinds of patients that would be put on the ventilator, whose permission had to be obtained to switch the patient to the ventilator being tested, and what would be said to patients and families about what we were

doing. We also wanted to describe a set of criteria that would define if and when the patients should be removed from the ventilators (prior to extubation). This resulted in a set of guidelines that are in Table 67.6. We wanted to limit the use of some of the ventilators’ advanced features because they were new and our clinicians were not experienced in how to use them. We felt this reduced potential risks to patients.

- We got initial push back from the manufacturers about the proposed scope of our clinical trial. Our goal was to ventilate 40–50 patients, and we thought this might take 1–2 months. To achieve this we required three ventilators. One of the manufacturer’s representatives dubbed our evaluation the “trial that would never end.”

Table 67.6 Sample protocol for clinical testing of a mechanical ventilator in pediatric and neonatal populations

1. The main goal during this clinical trial is to ensure patient safety and minimize the risk of application errors of the new ventilator being tested
2. Clinical testing will require manufacturers to produce at least three ventilators of each type being tested. One will be kept available for training, and two will be used on patients
3. Another important goal is to give as many properly trained respiratory therapists the opportunity to work with the ventilator and use it on as many different kinds of patients as possible
4. Training
4.1. Only those staff with ≥ 1 year of intensive care experience would be assigned a patient being ventilated with one of the ventilators being tested
4.2. No respiratory therapist may be assigned to a patient on this ventilator, or initiate the use of this ventilator unless they have completed the required training on the new device and completed the basic competency return demonstration
4.3. No training of ventilator operators will be done “just in time” at the bedside. Training will be structured and done in a controlled training area and done when the attendees are not on duty to minimize interruptions
5. Patient selection
5.1. We will attempt to study the ventilator’s performance on 10 patients in each of the following groups:
5.1.1. Neonates $\leq 1,200$ g

Table 67.6 (continued)

5.1.2. Infants >1,200 g ≤10 kg
5.1.3. Children ≥10 kg
5.2. Patients shall be selected in consultation with attending physician
5.3. Unstable patients will be excluded
5.4. Verbal consent from parents
5.4.1. Parents should be asked for their verbal consent to allow the new ventilator be applied to their child
5.4.2. They should be informed:
5.4.2.1. That this new ventilator is commercially available
5.4.2.2. That the benefits to their child may include advanced capabilities of the ventilator
5.4.2.3. That we are still gaining experience with the ventilator and that as a result there is a small increased risk to their child of ineffective ventilation but that their child will be very closely monitored while on the ventilator
6. Modes used: the ventilator has a large variety of modal combinations including adjustable flow cycling and tidal volume limitation with which clinical staff are not very familiar. To minimize risk to patients of misapplication, the following modes/features are to be used only with the consent of the attending physician and respiratory therapy supervisory staff
6.1. Flow cycling above 5 % in any mode
6.2. Volume-targeted decelerating flow in conjunction with volume limitation
7. Hours of the trial: patients shall be placed on the ventilator being tested only between the hours 0700 and 1300. Exceptions require the consent of the attending physician and the respiratory therapy supervisory staff
8. The following developments or conditions should be reported to the respiratory therapy supervisory staff immediately:
8.1. Any significant deterioration in blood gases that cannot be readily attributed to a non-ventilator-related cause
8.2. Any significant increase in spontaneous respiratory rate or other indication of increased agitation or work of breathing
8.3. Any significant increase in levels of ventilatory support or FiO ₂
8.4. Anytime a clinician is concerned that the ventilator might not be operating properly, the device should be removed and the patient placed on a ventilator from the extant fleet
9. All clinical staff who worked with the ventilator during the clinical trial are encouraged to fill out the ventilator evaluation survey (see Table 67.7)

67.2.5.1 Results of the Clinical Trial

The anecdotal evidence from the trial was positive but we were interested in getting a more quantifiable assessment of staff perceptions of the clinical trial. We constructed a survey instrument to measure the views of clinicians who used the ventilator (see Table 67.7). We used a 10-point ordinal scale, with declaratory statements with which the staff could rate the degree to which they agreed or disagreed. The survey was constructed to compare the ventilator being tested against the currently used ventilator. Results are depicted in Fig. 67.5.

Considering the complexity of such a clinical trial, there were some episodes of care during the trial that were very concerning. In two separate instances, the ventilator had been misapplied and temporary derangement of ventilation had occurred. In both cases, the respiratory therapists operating the ventilator were experienced, had completed all the required training, and demonstrated competency on the Avea. Both mishaps were deemed to have been caused by unfamiliarity with the device combined with applying new “advanced features.” These events serve as an important reminder that clinical evaluation of new ventilator technology is at once essential, complex, and potentially risky. But careful planning and execution can help to ensure a thorough evaluation and good final decision.

67.2.6 The Decision

It is said that you learn to make good decisions by making bad ones. It is hoped that through careful planning, testing, and analysis, you will not actually have to make a decision, which has been defined as “what you have to do when the data and evidence do not make your choice clear.”

There are systems and programs available to help in complex decision making. For the purposes of making a decision about a large capital purchases like a fleet of ventilators, there is an excellent resource available in form of the paper “Decision analysis for large capital purchases: how to buy a ventilator by Chatburn and Primiano (2001b).” This is an outstanding systematic approach such a complex decision.

Table 67.7 Sample clinical ventilator evaluation survey instrument

	New Ventilator Being Tested										Current Ventilator									
Date																				
Years of PICU or NICU/IICU Experience																				
Number of Shifts Worked with the Ventilator																				
Name (optional)																				
Please rate the ventilators on the following variables	Circle One										Circle One									
Size of the Ventilator:																				
The ventilator fit well at the bedside	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The ventilator was easy to move around	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
User Interface:																				
The ventilator was easy to learn	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The labeling of controls was easy to understand	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The terminology used on the ventilator was easy to understand	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
It was easy to adjust the ventilator	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
Features																				
The ventilator had all the modes I wanted in a ventilator	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
I understood all the modes on the ventilator	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The alarms were easy to adjust and reset	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The alarms had a distinctive sound that was easy to identify	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The alarm volume was loud enough	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The ventilator did not have a lot of nuisance alarms	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The volumes displayed by the ventilator were accurate	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
Patients seemed able to trigger the ventilator with relative ease	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The ventilator seemed to perform well in the presence of an airway leak	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The pulmonary graphics features on the ventilator were useful	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
Patients seemed able to trigger the ventilator with relative ease	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The likelihood of accidental changes of the ventilator settings is low	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									
The ventilator settings are easy to read in a low light environment	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
	Strongly Disagree ← → Strongly agree										Strongly Disagree ← → Strongly agree									

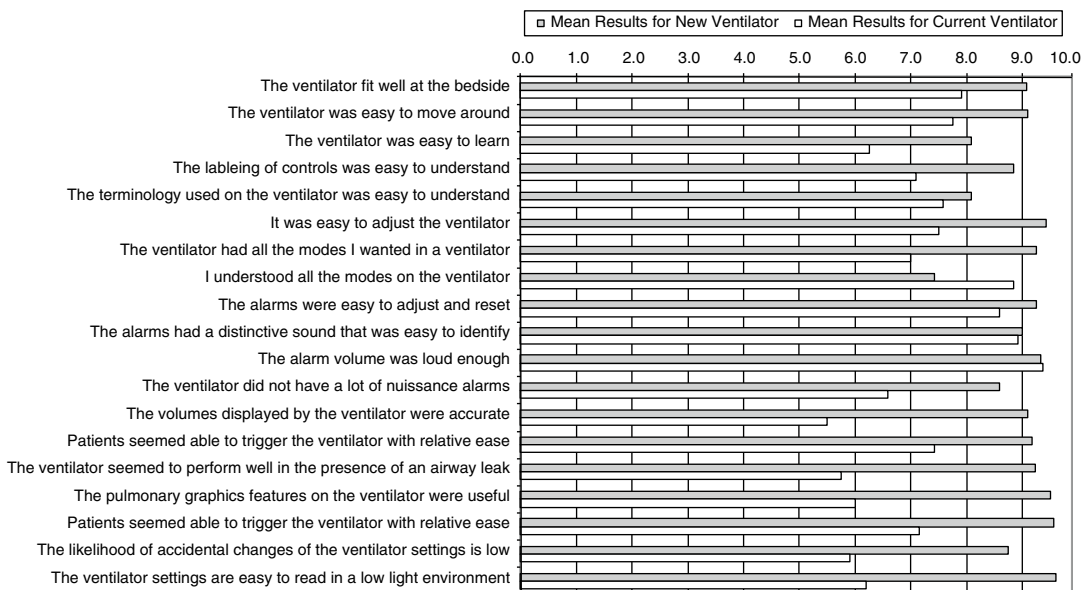


Fig. 67.5 Example of results of a survey of the clinical staff after the completion of a clinical trial of a new mechanical ventilator. Note that the instrument was

constructed as a comparative assessment of the new ventilator being tested versus the existing or current ventilator being used by the clinical staff

Another useful resource is the website www.ventworld.com. VentWorld describes itself as “....the Internet’s premier source of ventilator product and supplier information, news, discussion, education, tools, and vent resources for the respiratory and critical care community!” The website is operated by Amethyst Research LLC, which is a company that sells computer and web-based resources for acquiring and operating mechanical ventilators.

Essentials to Remember

- The most desirable features on a ventilator are dependant on local practice and culture.
- There are important performance differences between brands of ventilators used for neonatal and pediatric mechanical ventilators.
- All stakeholders should be involved early and often in ventilator evaluation planning and execution.
- Many ventilators used for neonatal and pediatric applications were not specifically designed for such applications.

- Bench testing is an essential part of any ventilator evaluation and can be readily accomplished with relatively inexpensive and simple measurement devices and lung models.
- More sophisticated evaluations of the patient-ventilator interface can be accomplished using more sophisticated active lung simulators.
- One of the most important features of neonatal and pediatric ventilators is the ability to accurately and precisely measure tidal volumes at the proximal airway. The need for such measures has now been extended into volumes <5 mL.
- Clinical use of ventilators is also an important part of any evaluation and should only be done with careful attention paid to patient safety, training, and competency. Just-in-time training at the bedside is to be avoided when evaluating new mechanical ventilators.
- Clinical evaluations should include a structured survey instrument.

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Part XXVIII

Organization and Management of Mechanical Ventilation Worldwide

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Educational Aims

With this chapter, the reader will be able:

- To describe the management of ventilation in several regions of the world
- To compare the education and role of caregivers in several regions of the world

There is little or no information available about the conditions in pediatric critical care units (PICUs) and a paucity of information on management of pediatric mechanical ventilation in North Africa. The aim of this section is to analyze the current reality of pediatric respiratory intensive care and to describe the practical aspects of mechanical ventilation management in Tunisia and Algeria, two North African countries part of the Maghreb, region in North Africa situated between the Mediterranean Sea, the Sahara, and Atlantic Ocean.

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68.1 Region's Profile and Child Health (Table 68.1)

Tunisia and Algeria are middle income and developing countries. Tunisia is North Africa's smallest country but, probably, the most socially advanced. Algeria, by contrast, is the largest North African country and the second largest country on the African continent.

Total population in the two countries is 44 million people, 27 % of whom are under 15 years of age (National Office of Statistics Algeria 2009; National Statistics Institute 2009). In the region, there are 11–13 physicians per 10 000 inhabitants compared with 2 per 10,000 in the rest of Africa and 32 per 10,000 in Europe (WHO 2009).

According to UNICEF's latest State of the World's Children report, under five and infant mortality rates, while low when compared with other African countries, are still relatively high, especially in Algeria (UNICEF 2009). Most of the child deaths occur during the neonatal period, as neonatal mortality represents 70–80 % of infant mortality and almost half of under five mortality (UNICEF 2009). In older children, the most common causes of death are diarrhea (13 %) and pneumonia (11–13 %) (UNICEF 2009).

Nevertheless, the region has achieved notable improvements in child health, over the last decades, particularly through reduction in mortality rates among infants and children. These improvements have been achieved through the control of communicable childhood diseases and promotion of maternal and child health programs.

Table 68.1 Tunisia and Algeria country profiles and principal indicators

	Tunisia	Algeria
Area (km ²)	154,630	238,174
Total population (thousands) 2008 (National Office of Statistics Algeria 2009; National Statistics Institute 2009)	10,326	34,800
Population <15 years (%) 2007 (National Office of Statistics Algeria 2009; National Statistics Institute 2009)	25	28
Under 5 mortality (per 1,000 live births) 2007 (UNICEF 2009)	21	37
Infant mortality (per 1,000 live births) 2007 (National Office of Statistics Algeria 2009; National Statistics Institute 2009)	18.7	26.2
Neonatal mortality (per 1,000 live births) 2004 (UNICEF 2009)	13	22
Life expectancy at birth 2007 (UNICEF 2009)	74	72
GNI per capita US\$ 2007 (UNICEF 2009)	3,200	3,620
Total expenditure on health (% of GDP) 2006 (WHO 2009)	5.1	4.2
Physicians density per 10,000 peoples 2000–2007 (WHO 2009)	13	11

However, there is a real need to deal with life-threatening illnesses and injuries and to develop and/or strengthen the capability to provide higher levels of care, to greatly influence patients' survival, and to reduce avoidable death.

68.2 Development of Pediatric Intensive Care in the Region

The ability to provide neonates and pediatric patients with prolonged mechanical ventilation for respiratory failure is relatively new in North African countries. Thus, neonatal and pediatric intensive care are still in their early development and are yet rudimentary.

In Tunisia, the year 1993 saw the establishment of the first 4-bed PICU within a general pediatric ward in the Children's Hospital of

Tunis. The first 12-bed PICU, with an independent department status within the hospital, was created in 1997. In order to achieve the United Nations' Millennium Development Goal 4 which is to reduce the under five mortality rate (United Nations 2008), national strategies are being implemented to reduce neonatal mortality which represents the vast majority of child deaths. As a result, the tertiary referral levels of newborn care are being strengthened by upgrading neonatology services of major university centers, enabling them to offer neonatal mechanical ventilation. In Algeria, the first PICU with a capacity of ten beds was established in 1996.

68.3 Pediatric Critical Care Resources

Material and human pediatric critical care resources are as yet extremely limited, and there is still great variation between cities, in the capability to provide critical care and mechanical ventilation. So, large number of neonates and pediatric patients requiring ventilation support do not have access to appropriate services. We can identify formal ICUs and informal pediatric acute and critical care beds.

68.3.1 Formal ICUs

There are only five NICUs and four PICUs, offering less than 100 beds in the two countries. All PICUs are mixed neonatal and pediatric ICUs, and most of them are mixed-function medical/surgical ICUs. For an under 15 years population of 2.5 million and 173,000 births annually (National Statistics Institute 2009), only four neonatal ICUs and one PICU, ranging in size from 4 to 12 beds, are available in Tunisia, three of which are located within the capital. In Algeria, which has an under 15 years population quadruple that of Tunisia and 704,000 births annually (National Office of Statistics Algeria 2009), there are one NICU and three PICUs, ranging in size from 8 to 16 beds, three of which are located within the capital.

There is much heterogeneity of performance of services which suggests that local management is a critical factor. Children can receive specialized respiratory critical care in some units, where advanced technology has become available, while some ICUs for pediatric patients are lacking in equipment and supplies and are inadequate to treat critically ill patients.

68.3.1.1 Caregiver Coverage and Role

The pediatric intensive care specialty is not yet recognized, and there are no board-certified pediatric intensivists. Only one Algerian PICU is staffed with medical anesthetists. In the two countries, NICUs are staffed with board-certified neonatologists.

Coverage by caregivers varies among the different units, depending on team's size, motivation, and leadership. Only one NICU and two PICUs have 24-h senior intensivist availability. Otherwise, there is 24-h pediatric resident availability with senior supervision on call.

The neonatologist or the pediatric intensivist is generally responsible for intubating patients; ventilator set-up and ventilation setting changes, according to the patient's status; and prescribing sedation if needed. He is also responsible for assessing the patient's respiratory status and evaluating weaning criteria on patients who may be extubated. Nevertheless, there is a greater likelihood that intubation and mechanical ventilation are provided by pediatric residents, as there are too few intensivists and no 24-h coverage by senior intensivists in the majority of ICUs. Intubation can be done by the anesthesiologist available in the hospital or by a trained nurse in only one NICU and one PICU.

Under normal circumstances, one nurse cares for two to three patients receiving mechanical ventilation. However, critical personnel shortages, in relation to limited financial resources and absenteeism, occur often in some ICUs, leading to low nurse/patient ratio and compromising safety of mechanical ventilation.

In well-organized ICUs, nurses are responsible for a large proportion of overall bedside work and are usually the primary health-care professional responsible for monitoring the patient's

respiratory status, as there are no respiratory therapists in our countries. They are responsible for documenting ventilator settings and spontaneous respiratory parameters every hour, performing suctioning and care of the airway, delivery of inhaled medications, and maintenance of the ventilator circuit. Nurses are also in charge of blood sampling for blood gas analysis.

As nurses are constantly present at the patient's bedside, they are responsible for providing immediate or urgent respiratory interventions (e.g., bag ventilation through endotracheal tube, bag-mask ventilation) and notifying the physician when acute deterioration of the patient's status occurs. They are also expected to respond to monitor alarms.

Except for fractional inspired oxygen (FiO_2), nurses are never allowed to change ventilation settings, as they, usually, do not have an adequate education background.

Contrary to most Algerian ICUs, Tunisian ICUs have, usually, an exclusive no full-time physiotherapist. The principal role of the physiotherapist is to provide positioning and therapy for secretion mobilization. The physiotherapist can also be involved in more specialized techniques and play an active role in extubation and in the implementation and surveillance of noninvasive mechanical ventilation.

68.3.1.2 Equipment

68.3.1.2.1 Respiratory Support Equipment

Although quality of respiratory critical care varies across services, in large measure depending on local management, all Tunisian ICUs are designated to deliver technologically advanced mechanical ventilation to the pediatric patients, as they are equipped with sophisticated and reliable mechanical ventilators. By contrast, among the four Algerian ICUs, only two ICUs have technologically advanced mechanical ventilation capabilities for neonates and children.

In the well-equipped ICUs, respiratory support equipment includes high-technology conventional ventilators, high-frequency oscillators, and noninvasive ventilators, especially nasal continuous positive airway pressure devices, in sufficient number. New treatment approaches for

respiratory failure, including inhaled nitric oxide (iNO), exogenous surfactant therapy, and high-frequency oscillatory ventilation (HFOV), are currently available, especially in Tunisian units. In the PICU of Children's Hospital of Tunis, about 80 % of all admissions require mechanical ventilation, and of the ventilated patients, almost 30 % are treated with HFOV because of refractory hypoxemia (Ben Jaballah et al. 2006).

Some Algerian ICUs are burdened with poor respiratory equipment, especially with respect to ventilators, despite the population's needs and the country's financial resources. Only two to three conventional ventilators are available in some 8- to 12-bed PICUs. The insufficient number of intensivists, the inadequacy of PICU nursing staff and the inability to ensure optimal care for critically ill patients, the lack of expertise on equipment operation and maintenance among the local distributors, and the hospital engineering department discourage some doctors from procuring respirators and high-technology equipment.

68.3.1.2.2 Monitoring Equipment

Portable clinical laboratory devices and mobile x-ray units used for bedside chest radiography are generally available.

Key ventilation parameters (e.g., FiO_2 , peak inspiratory pressure, tidal volume, mean airways pressure), graphic representation of pressure and flow curves, and continuous pulse oximetry and analysis of arterial blood gases are currently available. In some PICUs, arterial catheters are frequently utilized for rapid arterial blood gas analysis. Monitoring of pressures, tidal volume at the Y-piece in neonates and infants, are also available in most ICUs.

However, more complete ventilatory monitoring capability is generally lacking. Except for three ICUs, pressure-volume curve and flow-volume loops are not available. End-tidal PCO_2 concentration and transcutaneous PCO_2 in children are rarely used, and measurements of respiratory mechanics, dead space, and functional residual capacity are never used. High workload, insufficient staff training, and lack of equipment are the principal obstacles to performing such monitoring.

68.3.2 Informal Pediatric Critical Beds

Owing to the very limited number of dedicated neonatal and pediatric ICUs resources, critically ill pediatric patients are sometimes cared for and ventilated within the general pediatric wards. These settings are generally lacking in equipment, supplies, and skilled manpower and are inadequate to treat critically ill patients.

For surgical patients, mechanical ventilation is often provided in pediatric or mixed adult/pediatric surgical wards, under the responsibility of doctors who are generally trained in adult anesthesiology. In many wards, shortage of qualified staff and inadequate or lacking facilities to ventilate pediatric patients postoperatively lead to high perioperative morbidity and mortality rates, especially among neonates and infants. This problem is one of the most serious obstacles to developing specialized pediatric surgery, such as cardiac surgery, in our countries.

Furthermore, it is not uncommon that adult intensivists care for critically ill children when PICU care is not available.

Whatever their situation, variability in training and experience for pediatric intensive respiratory care and mechanical ventilation among physicians and nurses staffing these informal beds, frequently low nurse-patient ratios and inadequate equipment are serious obstacles to ensuring optimal and safe mechanical ventilation. As a result, despite its lifesaving potential, mechanical ventilation can add important morbidity and mortality risks in these wards.

68.4 Problems Encountered

Challenges facing pediatric critical care practitioners in our countries are multiple.

Availability of disposable equipment and maintenance of respirators in a functional state are continuous challenges to our ICUs. Although medication and equipment are generally available in teaching hospitals, problems with the supply of single-use airway devices, ventilator key consumables and spare parts,

as well as maintenance of equipment are common. There are often serious delays in the delivery of such material. This is due to the lack of local industry and the fact that imports continue to dominate the region's health-care market. Furthermore, financial resource constraints prohibit most hospitals from having their own stockpile of consumables and spare parts to meet their entire needs and prevent distributors from importing such equipment in sufficient quantities to meet hospital needs. This leads to shortages and frequent stock interruptions of ventilator consumables and spare parts, resulting at times in obstacles to ensuring the optimal practice of mechanical ventilation.

In addition to the material problems, the respiratory condition of many seriously ill infants and children arriving at ICUs had not previously been recognized. So, patients frequently exhibit severe respiratory failure or asphyxia upon admission, thus prolonging the required time at bedside. More acute interventions and provision of immediate or urgent medical interventions, such as intubation and chest drainage, are usually required upon arrival in the pediatric ICU because pediatric prehospital acute care is lacking, as there is no specialist retrieval team available.

The problems listed above affect the health professionals' availability to perform other medical functions such as quality improvement activities, development of protocols and procedures, and establishment of ICU-specific educational programs. Physicians usually spend too much time resolving nonmedical problems.

68.5 Educational Issues

The subspecialty of pediatric critical care is not officially recognized. As such, there is no national certification in pediatric critical care for

board-certified pediatricians and no residency training programs. The national pioneers in the specialty have obtained training abroad during several months or years.

Providing teaching about mechanical ventilation to fellows and residents is not always easy to do. Pediatric intensivists are generally overworked, as they spend too much time in the care of children at the bedside and in resolving many logistic problems.

Nurses have no special undergraduate or formal postgraduate pediatric critical care or mechanical ventilation training program and receive no special professional recognition, and this contributes to some lack of motivation.

The reality of mechanical ventilation in North African countries is far from the ideal vision. This illustrates the need to intensify our efforts to develop neonatal and pediatric intensive care and to make our neonatal and pediatric ICUs develop the capability to provide the contemporary standard of respiratory critical care. To reach these goals, more physical facilities, supportive technology, human resources, organization, and mostly willpower are needed.

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Christopher J.L. Newth and Philippe Juvet

Western countries have seen dramatic reductions in child mortality in the last century and overall improvements in child health with a neonatal mortality rate and an under 5 years old mortality rate below 10 per 1,000 live births (Goodman et al. 2002; WHO 2009). Neonatal and pediatric intensive care units and caregivers both play a role in this improvement. In Canada and USA, the management of critically ill newborn and children is done in two separate units with their own specific training programs and board certifications. The number of ICU beds is higher for neonates than for children (2–5.4 beds per 100,000 (Barry and Hocking 1994; Milne and Whitty 1995; Randolph et al. 2004) and 3.4 beds per 1,000 live births (Goodman et al. 2002),

respectively), so there are more NICUs compared to PICUs, but mechanical ventilation has similar organization in both.

69.1 Caregiver Coverage and Role

Most neonatal and pediatric intensivists are certified by the American Board of Pediatrics (Randolph et al. 2004), and most frequently, they are the primary physicians that provide care. In addition to the intensivist, patient coverage frequently involves residents and fellows. A 24-h, in-house coverage by an attending-level physician occurs in 37 % of PICUs (Table 69.1). Pediatric anesthesiologists and pediatric surgeons can also be the primary ICU physician if they complete a certificate of special competency in critical care. The physicians' role in the management of mechanical ventilation includes all aspects of mechanical ventilation.

The critical care nurse performs continuous bedside care, sometimes including the monitoring and modification of ventilation settings. Nurse-to-patient ratio is based on patient acuity, mechanically ventilated neonates and children usually have a 1:1 or 1:2 ratio. In a survey among PICUs across Canada and USA, nurses were involved in mechanical ventilation monitoring in 44 % of units and changed ventilator settings. In two-thirds, they set the inspired oxygen concentration, only.

Respiratory therapists are an integral part of bedside care in the PICU. They are trained in mechanical ventilation management. They take

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Table 69.1 Characteristics of PICUs in North America and caregiver coverage (survey in 30 PICUs across Canada and USA)

Number of beds in PICU (median (min, max))	20 (7, 45)
Number of physicians in PICU (median (min, max))	7 (4,20)
Medical staff with pediatric critical care training (median %)	100
Neonatal cases, cardiac surgery included (median % (min, max))	10 (0, 35)
Fellowship program in pediatric critical care medicine (%)	63
24-h on-site pediatric ICU attending coverage (%)	37

care of all ventilation aspects including operating and maintaining ventilators and managing pulmonary treatments (iNO, surfactant, inhaled medications). They adjust ventilator settings under the supervision of physicians. It is recommended by the American College of Critical Care Medicine and the Society of Critical Care Medicine to have in-house respiratory therapists available at all times. In practice, 90 % of PICUs have 24-h coverage (personal data), and some states mandate one respiratory therapist to a specific number of ventilated patients (usually between 4 and 6).

Physiotherapist performs chest manipulations, mobilization, incentive spirometry, and postural drainage. They usually do not take care of mechanical ventilation.

69.2 Recommended Equipment

In North America, PICUs and NICUs usually have approximately one conventional ventilator per bed. Nowadays, adult ICU ventilators are able to provide neonatal ventilation with similar performance, at least in term neonates, when compared to specific neonatal ventilators (Fontana et al. 2009). This reduces the need for

different types of ventilators being available in a hospital and simplifies respiratory therapist education. Noninvasive ventilation is performed either with specific flow-generating devices (especially in neonates) or with noninvasive ventilation mode of conventional ventilators.

In addition to conventional ventilators, there are two to six high-frequency oscillatory ventilators per unit depending on the unit size. Although improvement of outcome with high-frequency oscillatory ventilation when compared to conventional ventilation is not clearly demonstrated, this mode is used frequently in neonatal and pediatric ARDS (Cools et al. 2009; Henderson-Smart et al. 2009; Randolph et al. 2003), usually the so-called rescue therapy.

The use of cuffed endotracheal tubes, and the measurement of end-tidal CO₂, tidal volume, and airway pressures close to the Y-piece, is frequently done in clinical practice in North American units, but this is not the case for the measurement of dead space, residual capacity, and pulmonary volume at the end of expiration (Fig. 69.1).

69.3 Educational Issues

Ventilation protocols are not frequently used in PICUs (Santschi et al. 2007), and specific training in mechanical ventilation for junior doctors is not available in all intensive care units. There is evidence that clinical decision making with explicit protocols decreases practice variation between clinicians (Morris 2000) and improves practitioner performances (Garg et al. 2005). Ventilation decision-making standardization using explicit computerized protocols in specific disease states, e.g., ARDS/ALI or bronchiolitis/asthma, may help in the education of junior doctors, respiratory therapists, and nurses (see chapter on the subject).

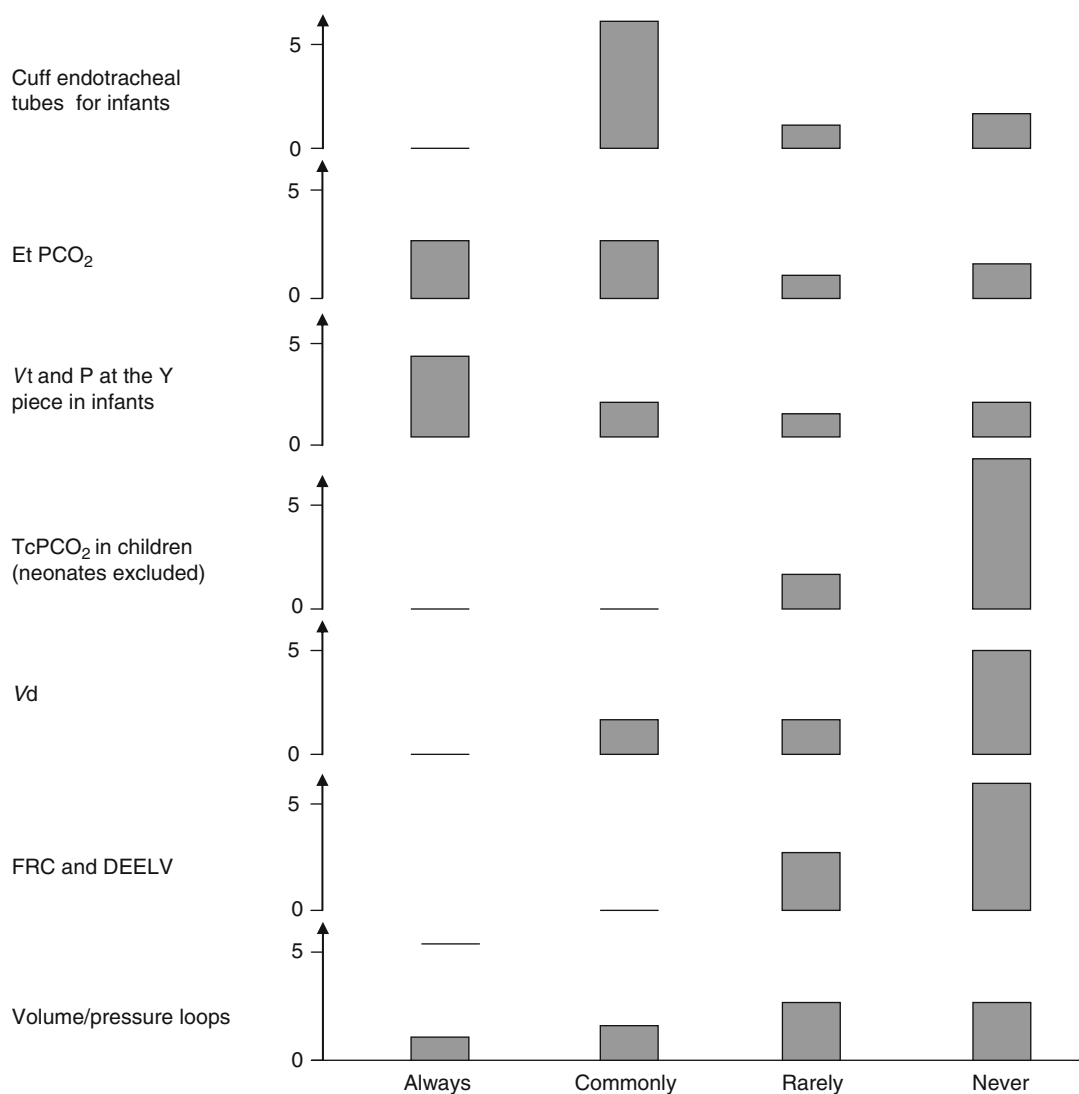


Fig. 69.1 Endotracheal tubes and monitoring equipment used in PICUs (survey in 9 PICUs across Canada and USA). *Et PCO₂* end-tidal PCO₂, *TcPCO₂* transcutaneous,

Vd dead space in the airway, *FRC* functional residual capacity, *DEELV* pulmonary volume at the end of expiration

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South America is a continent of uneven economic development, and this is reflected in pediatric intensive care units (PICUs) and the way they practice mechanical ventilation (MV). PICUs in countries which lack financial resources tend to be less technologically advanced, whereas those in wealthier nations can provide their patients with high-technology services and better quality care. In Guatemala, for example, the official data of the Panamerican Health Organization shows a rate of hospital beds per 1,000 inhabitants of 0.6, while in Brazil it is 2.4. As a standard of comparison, the rate in Canada is 3.4 and in the USA it is 3.1 (Organización Panamericana de la Salud. 2008).

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Although there has been global improvement in the quality of health care in South America in the last three decades, the severity and complexity of cases treated in PICUS has also increased. The survival rate of these cases is higher now than before, but so too is the number of patients who leave the hospital with chronic complex conditions requiring future hospitalization. This has been observed by Graham et al. (2004) in the USA, and it is particularly true in South America where, for cultural reasons, there are virtually no limits on vital support (Althabe et al. 2003; Piva et al. 2005), even in patients with severe chronic conditions who rarely benefit from intensive care.

Patients requiring intensive care have traditionally been divided into two categories: those that need monitoring in order to prevent rapid deterioration of vital status following major injuries (e.g., postoperative patients, especially cardiovascular) and those who require vital organ support (e.g., respiratory failure as the final stage of multiple diseases).

While in developed countries, most patients admitted to a PICU belong to the first group; in South America, the principal cause of admission is acute respiratory failure, and consequently, there is a greater need for MV. The percentage of patients who receive MV oscillates between 35 and 50 %, depending on seasonal variations, whereas, in developed countries, it ranges from 20 to 35 %. It is likely that this difference in the categories of patients who are submitted to MV explains in great part the different outcomes observed in several epidemiological studies carried out in both developed and developing

countries. An important study has shown that surgical patients receiving MV have a lower mortality rate than medical patients considering this a protective factor (Earle et al. 1997; Slater et al. 2003).

One aspect of particular interest here is data registry, without which, there cannot be adequate quality control. In South America, it is commonly not sufficient, and this together with the scarcity of reliable published information makes it necessary to depend on “grey literature” (low-quality journals, meeting reports, etc.) in order to form some idea of the epidemiology of MV in this part of the world, which unfortunately cannot be completely accurate.

One attempt to correct this problem is the “SATI-Q” project (<http://www.hardineros.com.ar/satiq/>), which has a pediatric arm that consists of a large database that summarizes the main outcomes and indicators of quality control in several PICUs in Argentina. This project is sponsored by “Sociedad Argentina de Terapia Intensiva,” the official society of both adult and pediatric intensive care in Argentina.

Although the rate of utilization of MV varies only slightly among the different countries on this continent, it varies significantly among the different PICUs within each country. This is due to the coexistence of public and private providers in the respective health-care systems. According to SATI-Q, the rate in Argentina is markedly higher in public than in private institutions.

There are a few published studies reporting rates of MV varying from 13 to 64 %. Most of these studies date from 5 or more years ago and only show the rate of utilization of invasive MV with minimum mention of noninvasive ventilation (NIV), which was less widespread at that time. The latter has been the topic of a few articles published recently (Prado 2005; Valenzuela et al. 2006), which we will discuss below.

70.1 Population Characteristics

Although there is little high-quality information in this field, some publications in small regional journals can give us a general idea.

70.1.1 Baseline Characteristics

Patient age tends to be similar – between 1 and 2 years – in studies on pediatric populations. In 1993, a large collaborative study by Saporiti et al. in Argentina (Saporiti colaborativo 1998) showed a median of 18 months, while a study in 1997 by Farias et al. (Farias 1999), which evaluated two samples of infants and children mechanically ventilated in two different seasons of the year, found a median of 14 months (IQR 4–14) in autumn and 5 months (IQR 2–12) in winter. Later, Moreno (2001–2002) (2005) reported a median of 12 months, and more recently, in 2008, Elorza Parra (2008) analyzed admissions data from 2001 to 2005 to arrive at a median of 24 months. The only study reporting specifically on the general characteristics of infants and children under MV was a 2004 epidemiological study by (Farias et al. 2004). It found a median age of 13 months (IQR 5, 48), a gender distribution similar to previous studies: female 40, 40.2, 31.6, and 40.7 % (Einloft 2002; Elorza Parra 2008; Moreno 2005), and a mean severity score (PRISM) of 13, which was similar to those of 16 (Moreno 2005) and 13.8 (Saporiti colaborativo 1998) reported by others. We should mention here that since the time of that study, PIM2 has been recognized as a better predictor (Eulmesekian et al. 2007), and today, PRISM is no longer used as a mortality score in our PICUs.

All the above studies showed a similar patient profile with respect to the primary problem, which was preponderantly medical (65, 76, 88, 73, and 73 %) (Einloft 2002; Elorza Parra 2008; Farias et al. 2004; Laphitz 2005; Saporiti colaborativo 1998), rather than surgical, and the presence of complex chronic conditions upon admission to the PICU varied only a little: 15 and 13 % (Elorza Parra 2008; Farias et al. 2004).

At this point, we see confirmed our previous assertion that in South America MV epidemiology is similar to general PICU epidemiology (age, gender distribution, severity score, and reason for admission).

70.1.2 Primary Reason for Mechanical Ventilation

Epidemiologic data shows that acute respiratory failure is by far the main reason for MV (72 %), followed by altered mental status (14 %), acute and chronic respiratory failure (9 %), and neuromuscular disease (1 %) (Table 70.1). With respect to acute respiratory failure, bronchiolitis and pneumonia are the primary causes, while, in acute and chronic respiratory failure, chronic obstructive disease after a viral infection is the leading cause.

70.1.3 PICU General Characteristics

The majority of PICUs in South America are medical-surgical and many of them also provide care to neonatal and pediatric patients. A partial report (Monteverde et al. 2008) from an ongoing study on MV in PICUs in Latin America and

Spain shows that, of 39 units analyzed, 39 % are in pediatric hospitals while 61 % are in general institutions; thus, 9 % of all pediatric beds are in PICUs. This result is double that of a study with a similar methodology carried out 8 years ago (Farias et al. 2004), which obtained a rate of approximately 4 %.

Although as noted previously, the rate of utilization of MV varies greatly between units, particularly in small series (from 8 to 64 %) (Duarte Vilariño 2006; Lopes Riccetto 2006; Slater et al. 2003). However, there is no such variation between large and multicenter studies: 44 % (Farias et al. 2004) vs. 45.4 % (Monteverde et al. 2008), which is in accordance with data from the SATI-Q report: 41.6 % (Ratto et al. 2007). Almost all institutions report providing intermediate care.

70.2 Caregiver Coverage and Role (Tables 70.2 and 70.3)

Table 70.1 Primary reason for mechanical ventilation

Year	1997 (Farias 1999)	1999 (Farias et al. 2004)	2007 (Monteverde et al. 2008)
ARF; <i>n</i> (%)	65 (63)	526 (79)	773 (80)
ARDS; <i>n</i> (%)	6 (9)	16 (3)	32 (4)
Bronchiolitis; <i>n</i> (%)	18 (28)	35 (7)	275 (36)
Pneumonia; <i>n</i> (%)	15 (23)	100 (19)	164 (21)
Septic shock; <i>n</i> (%)	6 (9)	70 (13)	125 (16)
Postoperative; <i>n</i> (%)	11 (17)	161 (31)	32 (4)
Other; <i>n</i> (%)	9 (14)	144 (27)	145 (19)
CRF; <i>n</i> (%)	14 (13)	51 (8)	54 (6)
Altered mental status; <i>n</i> (%)	13 (13)	87 (13)	131 (14)
Neuromuscular; <i>n</i> (%)	12 (1)	6 (1)	10 (1)

Table 70.2 Caregiver coverage of mechanical ventilation in different countries of South American PICUs. MV: mechanical ventilation

Country	Pediatric intensivist 24 h/day	PIC fellow 24 h/day	Patients/nurse (<i>n</i>)	Respiratory therapist	Physio therapist	ARDS protocol	Weaning protocol	Sedation protocol	Training in MV for fellows	Training in Mechanical ventilation for nurses
Argentina	Y	Y	2	N	Y	Y	Y	Y	Y	Y
Honduras	Y	Y	4	Y	Y	Y	Y	Y	N	N
Costa Rica	Y	N	3	Y	Y	N	N	N	Y	N
Colombia	Y	N	2.5	Y	Y	N	N	N	Y	Y
Chile	Y	Y	3	Y	Y	N	N	N	Y	Y
Brazil	Y	Y	1	Y	Y	N	N	N	Y	Y
Total	100 %	66.6 %	2.6	83.3 %	100 %	33.3 %	33.3 %	33.3 %	83.3 %	66.6 %

Table 70.3 Respiratory support equipment for mechanical ventilation in South American PICUs

Country	PICUs (n)	Private/public/Both	Beds in each PICU (n)	Intermediate care	Conventional ventilators in each PICU (n)	HFOV ventilators in each PICU (n)	Noninvasive ventilators in each PICU)
Argentina	100	Both	5–36	Yes	6–20	1–2	6–20
Chile	28	Both	6–14	Yes	4–12	1–2	1–12
Colombia	120	Both	10–15	Yes	10	1–2	10
Honduras	2	Public	16	Yes	20	0	0
Costa Rica	1	Public	22	No	30	6	30
Brazil	1,000	Both	10–12	No	10–18	1–2	1–2

70.2.1 Medical Doctor

In Brazil, Chile, Costa Rica, and Argentina, medical doctors, PIC fellows, and residents are the personnel in charge of intubating patients. In Colombia and Honduras, where there are no fellowships, medical doctors and residents are in charge of this. In some centers, the anesthesiologist is also included.

In all cases, it is the physician who makes decisions about MV (initiation, setting changes, monitoring, weaning).

70.2.2 Nurses

The reported ratio of patients on MV/nurse is about 2.6–1 (ranging from 1 to 4). In the countries mentioned above, our survey shows that roughly half of all nurses receive continuous training in MV. Besides basic care, these nurses are principally responsible for monitoring mechanically ventilated patients. Only in Costa Rica were additional responsibilities reported.

70.2.3 Respiratory Therapist

In South America, the respiratory therapist monitors MV and weaning. In Costa Rica, however, respiratory therapists prescribe and set the changes in MV.

70.2.4 Physiotherapist

In South America, the terms “physiotherapist” and “respiratory therapist” refer to the same professional.

70.3 Recommended Equipment

70.3.1 Respiratory Support Equipment

PICUs in South America generally have approximately one conventional microprocessed ventilator per bed, one or two high-frequency oscillatory ventilators per unit, and one noninvasive ventilation device for every two beds.

In Chile, investigators have reported a remarkable increase in the use of NIV. A survey-based study by Valenzuela et al. (2006) of 21 units, public and private, shows that more than 80 % provide this therapy, 55 % with special devices designed for the purpose, and the rest with conventional ventilators. The median rate of utilization, as expressed by patients in NIV per 1,000 bed days, is 27.6 (range 9.6–62.3), and the principal diagnoses at admission are asthma and pneumonia/pneumonitis.

70.3.2 Interfaces

As seen in two nonselected cohorts of pediatric patients (Farias 1999; Monteverde et al. 2008), the interface generally used to deliver gas in conventional MV is the endotracheal tube (78 and 96 %) and via orotracheal intubation (63 and 87 %, vs. nasal, 37 and 13 %). With the exception of Colombia, Brazil, and Argentina, the use of cuffed endotracheal tubes is uncommon. In these cohorts, the presence of a tracheostomy as the interface for MV was very low, but over the past few years, there has been an increase in its

utilization in patients expected to require MV for 3 weeks or longer (Plummer and Gracey 1989). According to a recent survey-based study by Principi et al. (2008), 51 % of physicians surveyed believe tracheostomy is an underutilized technique in pediatrics. As noted by Da Silva et al. in an epidemiological study on pediatric patients tracheostomized while on MV (Da Silva et al. 2005), it seems that, unlike adults (Frutos-Vivar et al. 2005), pediatric patients who require a tracheostomy do not have worse prognoses in the acute setting (estimated by mortality scores), but do have a higher long-term mortality rate, which is probably a result of in-hospital complications.

With respect to NIV, the oronasal mask is the preferred interface by medical teams in PICUs, in spite of the availability of others (Valenzuela et al. 2006). Nasal masks are mainly used in older patients with chronic diseases (Prado 2005).

70.3.3 Ventilator Modes and Setting

The 2004 study by Farias et al. (2004) found that the most commonly used modes of MV were synchronized intermittent mandatory ventilation alone or combined with pressure support ($n=257$; 39 %; 95 %, CI 35–43), followed by pressure control ventilation ($n=166$; 25 %; 95 %, CI 22–29), and volume limited ventilation (assisted/controlled) ($n=165$; 23 %; 95 %, CI 20–26). There was a high crossover incidence: 53 % of the patients received more than one ventilator mode during the study period. It is noteworthy that there were no differences in ventilator mode utilization rates among the different categories of respiratory failure.

This reality of 5 years ago has recently given way to a higher utilization of assist/control modes (either pressure or volume limited, or even both, in dual modes) until criteria for disconnection are met, after which a spontaneous breathing trial is performed (either with a T-piece or with pressure support of less than 10 cmH₂O or CPAP of 5 cmH₂O or less). At the Latin American Pediatric Intensive Care Congress in 2008, the following results were reported (Monteverde et al. 2008):

SIMV with or without PSV: 12.5 %, A/C-VLV: 19.5 %, and A/C-PLV: 57.1 %.

Although the use of NIV has increased over the last 5 years, this increase has not been as great as some self-reported data lead us to believe it would be (1.5 % vs. 5.6 %) (Farias et al. 2004; Monteverde et al. 2008).

70.3.4 Monitoring Equipment

Self-reporting leads us to believe that the measurement of end-tidal CO₂, auto-PEEP, plateau pressure, as well as the display of volume/pressure curves is widespread in South American units, but this is not the case with the measurement of tidal volume and airway pressures close to the Y-piece, nor is it true for dead space in the airway, which few units have reported measuring. Transcutaneous CO₂ is not reported to be in use in any center, nor is the measurement of residual capacity and pulmonary volume at the end of expiration.

70.4 Educational Issues

Most units reported being staffed by doctors, nurses, and physiotherapists or respiratory therapists certified in pediatric intensive care. In almost half the countries consulted, there are full-time residences and fellowships in pediatric intensive care medicine and training programs in MV. Less common are training programs in MV for nurses. In all countries except Honduras, there is a low use of protocols (Table 70.2).

70.5 Outcome

Mean duration of MV, independent of the indication, is about 5–7 days. In the 2004 study of Farias et al., it was found that in 1999 the time between the moment the patient meets the criteria for disconnection and the moment he was really extubated as high as 46 % of total ventilatory support – about 2–3 days (Farias et al. 2004). It is important to note that there has been a change

in medical behavior over the past 5 years with respect to the last phase of MV, the one prior to disconnection. The strategy for weaning pediatric patients from MV has shifted from a gradual reduction of ventilatory support (GRVS), in which there is a reduction of respiratory frequency in SIMV or a reduction of pressure support in PSV, towards the performance of a spontaneous breathing trial (SBT) after the patient has met the criteria for sustained spontaneous ventilation (see related chapter): in the study of 2004 (Farias et al. 2004), the use of GRVS compared to SBT was 66 % vs. 31 %, and more recently (Monteverde et al. 2008), GRVS vs. SBT was 16 % vs. 76 %. This reveals a clear impact on the duration of ventilator support: the performance of SBT results in a mean duration of 7.3 days, while it is 8.9 days for GRVS.

The average length of stay in South American PICUs is about 8–10 days, with 80 % of total time under MV (Farias et al. 2004; Ratto et al. 2007). There is little data available on complications related to MV, but we do know that the rate of ventilator-associated pneumonia is 9.75 episodes per 1,000 ventilator days (Ratto et al. 2007), while that of pneumothorax is 8.7 % (Elorza Parra 2008).

With respect to mortality, different studies report rates varying from 10 to 20 % (Farias et al. 2004; Ratto et al. 2007; Saporiti colaborativo 1998; Elorza Parra 2008). When we compare the mortality rates in patients on MV in private and public hospitals, the former are lower than the latter. Thus, private institutions have a good correlation with PIM scores, and a mortality rate that is lower than predicted, whereas public hospitals show a higher than predicted rate (Ratto et al. 2007). Mortality is different for each group of patients considering their reasons for MV, being significantly higher among those with ARDS or altered mental status than among those with acute respiratory failure or acute and chronic respiratory failure (Farias et al. 2004), and also higher in those patients requiring reintubation when compared to those successfully extubated after planned extubation (19 % vs. 5 %) (Farias et al. 2004).

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Francis Leclerc

Mechanical ventilation is the principal technology that justifies admission of critically ill patients in intensive care units (children (www.picanet.org.uk) as well as adults (Metnitz et al. 2009)). In a recent survey conducted in France in 2002 by the French Ministry of Health that included 40 intensive care units for children (30 caring for neonates and children (N-PICUs), 10 caring only for children older than 1 month (PICUs)), 24 units completed the item “mechanical ventilation” for a total of 14,147 admissions. In total, 47 % of patients were mechanically ventilated (30 % with a duration of more than 48 h) (Table 1.1. data not published). This percentage is close to the 40–45 % reported in the Netherlands (Dahlem et al. 2003; Kneyber et al. 2008) and 49 % in Italy (Wolfler et al. 2010) and higher than that recently reported in 16 US pediatric ICUs (30 %; range 20–64 %) (Khemani et al. 2009), but lower than the 73 % reported in the UK for 2008 (www.picanet.org.uk). Also, respiratory diseases or dysfunction represent the most frequent cause of ICU admission either for neonates (Janota et al. 2008) or children (Johnston et al. 2004; Leteurtre et al. 2003). In a recent report of 51,386 children with organ dysfunction, respiratory dysfunction was the strongest predictor of death and was associated with a greater than

5-fold increase in length of stay and a 25-fold increase in total charges (Johnston et al. 2004). Finally, number of ventilation-free days is utilized as an outcome measure in clinical trials assuming that the decrease in duration of ventilation benefits the patient and reduces treatment costs (Curley and Zimmerman 2005).

Patterns of practice of mechanical ventilation in neonatal and pediatric ICUs have been reported in the past for the USA (Harel et al. 1998; Salyer and Chatburn 1990) and other countries, such as Argentina and Spain (Farias et al. 2004) and Italy (Wolfler et al. 2010), but data regarding organization and management of mechanical ventilation in European neonatal and pediatric ICUs are remarkably scarce. Thus, we surveyed by e-mail, at the beginning of 2009, the PICUs affiliated with the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) and/or participating to the Pediatric Acute Lung Injury Mechanical Ventilation strategies (PALIVE) study (Santschi et al. 2010). Among the 27 European countries, 13, representing 20 ICUs, completed our survey.

71.1 Results of the Survey

71.1.1 Caregiver Coverage and Role (Tables 71.1, 71.2, 71.3, 71.4, and 71.5)

A nurse cares for 2 children in 12 (60 %) units, for 1 in 5 (25 %) units, for 3 in 2 (10 %) units, and for four or more in 1 (5 %) unit.

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Table 71.1 Percentage of children mechanically ventilated (with indication of those ventilated more than 48 h) in 24 French NICU-PICU (17) and PICU (7) during 2002

	% of mechanically ventilated children			% of mechanically ventilated >48 h		
	Total	N-PICUs	PICUs	Total	N-PICUs	PICUs
Mean	47	48	45	30	30	28
Median	43	46	41	26	26	28
1st quartile	37	34	40	24	25	19
3rd quartile	61	64	54	37	38	36
Maximum	80	80	68	44	44	42
Minimum	20	20	21	13	14	13

N-PICUs neonatal and pediatric intensive care units, *PICUs* pediatric intensive care units

Table 71.2 Caregiver coverage

	Yes <i>n</i> (%)	No <i>n</i> (%)
Is a pediatric intensivist in-house 24 h a day?	9 (45 %)	11 (55 %)
Is a fellow in-house 24 h a day?	14 (70 %)	6 (30 %)
Is at least one respiratory therapist available in the unit?	2 (10 %)	18 (90 %)
If yes, is he (she) present 24 h a day?	0 %	2 (100 %)
Is a physiotherapist available?	18 (90 %)	2 (10 %)
If yes, is he (she) available 24 h a day (on call or in-house)?	5 (28 %)	13 (72 %)

Table 71.3 Caregiver(s) who intubate(s) the children in the PICU

	<i>n</i> (%)
Pediatric intensivist	20 (100 %)
Fellow in pediatric intensive care	18 (90 %)
Resident in the unit	14 (70 %)
Anesthesiologist present in the hospital	10 (50 %)
Trained nurse	1 (5 %)
Respiratory therapist	NA

NA not applicable

Table 71.4 Involvement of caregivers in mechanical ventilation during acute illness

	Prescription of ventilation (%)	Settings modification on the ventilator (%)	Ventilation monitoring (%)	Ventilation weaning (%)
Medical doctor	100	100	90	100
Nurse	0	45	95	40
Respiratory therapist	0 ^a	0 ^a	0 ^a	0 ^a
Physiotherapist	0	0	10	15
Parents	0	0	0	0
Others	0	0	5	0

^a2 N-PICUs and PICUs have a respiratory therapist

Table 71.5 Utilization of protocols

	Yes <i>n</i> (%)	No <i>n</i> (%)
Is it frequent to use a protocol that allows caregivers to change ventilation settings in the absence of prescription (delegation of treatment)?	5 (25 %)	15 (75 %)
If yes, which kind of protocol is it (select all applicable)?	<i>n</i> (%)	
ARDS protocol	2 (40 %)	
Weaning protocol	4 (80 %)	
Sedation protocol	3 (60 %)	
Other protocol (Specify)	0 %	

71.1.2 Equipment and Monitoring (Tables 71.6 and 71.7)

The most commonly measured parameters were volumes and pressures at the y piece in infants, and EtCO₂. Other parameters, such as TcPCO₂ (excluding neonates), dead space, end-expiratory lung volume, and functional residual capacity,

were rarely measured, while volume/pressure loops were monitored commonly (or always) in 13 ICUs (65 %). Other mentioned parameters were compliance (4 ICUs), auto-PEEP (Bachman et al. 2008), work of breathing, resistances, tubing compressible volume, time constant, and low-flow inflation pressure-volume curve (1 for each).

Table 71.6 Respiratory support equipment

Country (number of responses)	How many PICUs in your country? n/million of inhabitants ^a	How many beds in a standard PICU?	How many ventilators with conventional modes in such a PICU? n/bed	How many ventilators with high-frequency oscillatory ventilation in such a PICU? n/unit	How many ventilators dedicated to noninvasive MV in such a PICU? n/unit
Belgium (2)	0,8	6–14	0.5–1	1–4	1–10
Denmark (1)	4,9	8–15	1	0–2	1–4
Finland (1)	0,76	5–10	1	2–5	2–7
France (2)	0,68	2–20	1	1–6	0–3
Germany (1)	0,48	8–12	1	1–3	2–6
Ireland (1)	0,47	9–15	1	2–4	1–5
Italy (1)	0,25	5–8	1	1	1–2
Spain (3)	1,25	5–15	1	0–2	1–4
Sweden (1)	1,5	6–12	1	1–2	0–8
Switzerland (1)	0,77	6–18	0.5–1	1–6	0–4
The Netherlands (1)	0,5	6–14	1	0–2	2–4
UK (2)	0,48	6–12	1	1–3	4–5

^aSource for population: <http://cbandiera.free.fr/europe/index.php>

Table 71.7 Monitoring equipment

	Always n (%)	Commonly n (%)	Rarely n (%)	Never n (%)
Do intensivists use cuffed endotracheal tubes for infants?	0 (0 %)	8 (40 %)	10 (50 %)	2 (10 %)
Are tidal volume and pressures measured at the Y-piece in infants?	6 (30 %)	7 (35 %)	6 (30 %)	1 (5 %)
Do intensivists monitor EtCO ₂ ?	5 (25 %)	11 (55 %)	4 (20 %)	0 (0 %)
Do intensivists monitor transcutaneous PCO ₂ in children (neonates excluded)?	0 (0 %)	3 (15 %)	10 (50 %)	7 (35 %)
Do intensivists measure dead space?	1 (5 %)	2 (10 %)	14 (70 %)	3 (15 %)
Do intensivists measure Δ end-expiratory lung volume (Δ EELV)?	0 (0 %)	0 (0 %)	11 (55 %)	9 (45 %)
Do intensivists measure functional residual capacity (FRC)?	0 (0 %)	0 (0 %)	9 (45 %)	11 (55 %)
Do intensivists monitor volume/pressure loops?	3 (15 %)	11 (55 %)	3 (15 %)	3 (15 %)

71.1.3 Educational Issues (Table 71.8)

Table 71.8 Educational issues

	Yes <i>n</i> (%)	No <i>n</i> (%)
Do senior intensivists have certification in pediatric critical care medicine?	18 (90 %)	2 (10 %)
Do junior doctors (fellows and residents) in PICUs have specific training in MV?	19 (95 %)	1 (5 %)
Do nurses working in PICUs have specific training in MV?	15 (75 %)	5 (25 %)

MV mechanical ventilation

71.2 Conclusion and Proposals

It appears that organization and management of mechanical ventilation varies across the different European countries. Nevertheless, the percentage of mechanically ventilated children seems higher in Europe than in the USA, and the nurse staffing ratio is rarely 1/1 (5 % of ICUs). An important difference with North American organization is the absence of respiratory therapists in all except two European ICUs.

Unfortunately, our survey has some limitations: we only obtained information from 13 of 27 European countries (48 %), and the questionnaire did not distinguish neonatal and pediatric practices of mechanical ventilation.

A nice challenge for ESPNIC in the near future would be to promote expert consensus conferences and recommendations with the aim of defining the precise role of each caregiver working in N-PICUs and PICUs, to recommend equipment and monitoring protocols for the different ventilation strategies (Kissoon et al. 2008) and to organize education workshops for nurses and physicians (one such workshop was held in the 20th ESPNIC medical and nursing congress in Verona-Italy). Note that caregivers who attend such workshops and meetings are probably, using the Rogers' approach, "pioneers" and "early-adopters" of new technologies (Bachman et al. 2008). Several initiatives have been taken in Europe by scientific societies. For example, the European Society of Intensive Care Medicine (ESICM) has developed the PACT (Patient-centered Acute Care Training) program, which is a modular multidisciplinary distance-learning program aimed at improving and harmonizing the quality of acute

care medicine that contains 44 modules covering the ICU curriculum; three modules relate to respiratory failure, mechanical ventilation, and respiratory monitoring and include some pediatric particularities (<http://www.esicm.org/Data/ModuleGestionDeContenu/PagesGenerees/03-education/OB-pact-programme/25.asp>). Also, the French Society of Intensive Care medicine (SRLF) has organized expert or consensus conferences including pediatric aspects of monitoring of mechanical ventilation (Experts' consensus (Leclerc 2000; Leclerc and Nève 2000)), ARDS (Experts' consensus (Dauger et al. 2005; Richard et al. 2005)), noninvasive mechanical ventilation (consensus conference: <http://www.srlf.org/Data/ModuleGestionDeContenu/application/375.pdf>), and weaning from mechanical ventilation (consensus conferences) (Boles et al. 2007; Durand and Devictor 2001). One of the main objectives for caregivers starting mechanical ventilation is to avoid ventilator-induced lung injury in children suffering (Marraro 2005) or not suffering (Schultz 2008) from acute lung injury, even though recent laboratory data suggest that neonatal and infant lungs are less – not more – vulnerable to the effects of high VT (Albuali et al. 2007). Thus, weaning from mechanical ventilation is the goal (Leclerc et al. 2010). Intelligent decision support systems adapted for ventilation (including weaning) may be helpful to improve treatment decisions and reduce the workload of ICU caregivers (Tehrani and Roum 2008). Another important aspect of mechanical ventilation management is represented by ventilator-associated pneumonia (VAP), which is the second most common hospital-acquired infection (occurring in about 5 % of mechanically ventilated children); Bigham et al. recently

demonstrated that implementation of a specific prevention bundle produced a sustained reduction in VAP rate (from 5.6 to 0.3 infections per 1,000 ventilator days; $p < 0.0001$) (Bigham et al. 2009). The European community has launched a surveillance program in this domain (Dubos et al. 2007). Finally, noninvasive ventilation that may be beneficial for children with acute respiratory failure, preventing complications associated with invasive ventilation and avoiding reintubation when applied immediately after extubation, is being increasingly used in European PICUs (Calderini et al. 2010; Essouri et al. 2006; Mayordomo-Colunga et al. 2010; Mayordomo-Colunga et al. 2009; Munoz-Bonet et al. 2010; Noizet-Yverneau et al. 2010; Piastra et al. 2009; Wormald et al. 2009). In conclusion, organization and management of mechanical ventilation justify the pursuit of the work initiated in 2002 by the Multidisciplinary Joint Committee of intensive Care Medicine created, with the help of ESICM, by the European Union of Medical Specialists (UEMS) in which there is a pediatric section (De Lange et al. 2002). This group has worked out a definition of intensive care, a framework for education and training, continuing medical education, and criteria for accreditation (De Lange et al. 2002).

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Oceania traditionally comprises Australia, New Zealand, Polynesia, Melanesia, and Micronesia. This includes diverse geography from sparsely populated desert inland with communities living hundreds of kilometers from each other, to densely populated cities with significant infrastructure and congestion problems. Isolated islands with rudimentary intensive care services share the region with sophisticated neonatal and pediatric intensive care units. While Australia and New Zealand are fortunate to have well-organized and well-resourced intensive care units with efficient transport systems, services providing intensive care to babies and children in countries such as Papua New Guinea, Fiji, and smaller islands are much more limited. Interactions between different regions in Oceania are also complicated, and many critical care services, such as cardiac surgery, are provided to many countries in Oceania by volunteer groups and Australian and New Zealand government aid. Provision of critical care in Australia and New Zealand is in some ways indistinguishable from those provided in Europe and North America, while those available to children in Polynesia, Melanesia, and Micronesia may be more akin to those in sub-Saharan Africa.

Due to its huge area and distances between centers, provision of care to isolated communities in Australia, particularly indigenous communities, is significantly impeded. While Australia and New Zealand are two of the most urbanized countries in the world, only 30 % of the indigenous population live in major cities with rapid access to tertiary medical services. As the life expectancy of indigenous persons is lower than other Australians, approximately 39 % of the indigenous population are less than 14 years of age (Australian Bureau of Statistics 2009) (Fig. 72.1).

72.1 Neonatal Services

Neonatal services providing ventilation in Australia and New Zealand range from being extremely centralized in some areas (e.g., Western Australia) to being more fragmented with many smaller units caring for larger populations (e.g., New South Wales). While there is some crossover between neonatal and pediatric intensive care, there is only one combined PICU/NICU in Australia and New Zealand.

There are 28 level III neonatal nurseries in Australia and New Zealand. Level III nurseries are those that care for ventilated babies. These nurseries are of varying size – King Edward Memorial Hospital in Western Australia has 105 cots which service the entire population of Western Australia, while, for example, Sydney Children' Hospital (which also has PICU beds) has four cots. New South Wales with a population of six million is

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Fig. 72.1 Map of Oceania

covered by nine neonatal units, while WA, with two million people, has one. New Zealand has six units widely spread across the country. While many of these units are attached to or part of maternity hospitals and hence receive most admissions directly from the delivery suite, others are part of pediatric hospitals and receive admissions directly from the emergency department or transport services. Approximately 8,000 babies were admitted to level III nurseries in 2006. This represents 2.2 % of all live births in Australia and New Zealand. Of these babies, 45.6 % were less than 32 weeks gestation. Almost all of these babies required some form of assisted ventilation, either invasive ventilation or CPAP. Overall 91.3 % of babies admitted to level III neonatal nurseries in Australia and New Zealand required assisted ventilation at some stage during their admission.

Of the 7,591 babies requiring assisted ventilation, 47 % required invasive ventilation, 76 %

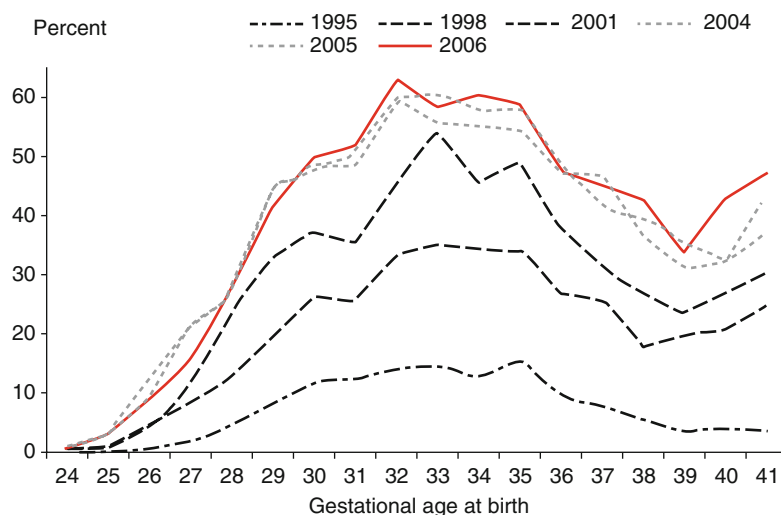
required noninvasive ventilation, and 6–7 % required high-frequency ventilation (HFV). Invasive ventilation, including HFV, was much more frequently used in babies of lower gestational ages, although even at gestational ages of 26–27 weeks, noninvasive ventilation was still commonly used (50 %) (Australian and New Zealand Neonatal Network 2006).

Trends over the last 10 years (Fig. 72.2) demonstrate that the use of CPAP has increased markedly.

The use of HFV in babies born less than 28 weeks has been stable for the last 7 years after a dramatic increase in use in 1999. Since then, about 25–30 % of babies born less than 28 weeks gestation received HFV.

The use of inhaled nitric oxide however has continued to increase since 1997 with about 8 % of babies, both preterm and term, being given nitric oxide in 2006.

Fig. 72.2 Trends in the use of CPAP as the only form of ventilation by gestational age (From Australian and New Zealand Neonatal Network 2006, published with permission)



72.2 Pediatric Services

Pediatric critical care services in Australia and New Zealand are among the most centralized in the world. The entire pediatric population of Australia and New Zealand are serviced by eight full-time pediatric intensive care units across the country. Australia is divided up into seven states and territories, and each state/territory provides transport services to its region.

Over 8,000 children are admitted to intensive care each year in Australia and New Zealand, the majority being at eight full-time pediatric units. Of those patients, over half are mechanically ventilated on admission to intensive care. Although most children are cared for in dedicated PICUs, 14 general intensive care units also admit children throughout Australia and New Zealand. The median length of stay for mechanically ventilated patients was 2.17 days (Australian and New Zealand Paediatric Intensive Care Registry 2007).

In Australia, all major capital cities are serviced by a specialized PICU. In Tasmania, Australian Capital Territory and the Northern Territory; however, the population cannot sustain these stand-alone services, and children in these areas are either cared for in adult ICUs or transferred to PICUs in other areas. In New Zealand, the demographics are a little different in that only

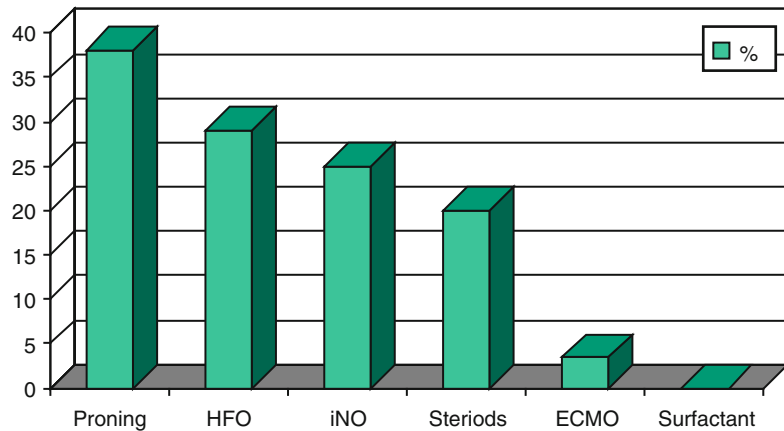
one city, Auckland, has a substantial enough pediatric population to maintain a stand-alone pediatric ICU. There are, however, a number of larger cities with substantial populations on both the north and south island of New Zealand, and children in these areas are generally cared for in adult ICUs or transferred to Auckland if tertiary pediatric critical care (e.g., cardiac surgery) is required.

The case mix requiring mechanical ventilation in Australia and New Zealand has altered over the past decade. Although the burden from some disease has probably lessened due to improving living conditions, better preventative measures against injury and infection and improved primary medical care, other conditions requiring mechanical ventilation have increased. More complex surgical procedures particularly surgery for congenital heart disease and more aggressive support of patients with chronic or progressive conditions have contributed to maintain the need for ventilatory support in children.

Of the children admitted to specialized pediatric intensive care units, over half are mechanically ventilated with ventilation rates ranging from 35 to 73 % in tertiary pediatric ICUs.

While there have been no surveys looking at mechanical ventilation in general, in Australia and New Zealand, the recently published lung injury survey looked at details of mechanical ventilation of children with acute lung injury in

Fig. 72.3 Use of adjunctive therapies in pediatric intensive care (From Erickson et al. 2007)



Australia and New Zealand over a 12-month period (Erickson et al. 2007).

In children with acute lung injury, the most common mode of ventilation was SIMV (51 %), followed by PRVC (20 %). High-frequency oscillation was the initial mode used in 12 % of patients with ALI but was used in 29 % of these patients during their admission in ICU.

In patients with ALI, the use of adjuncts to mechanical ventilation was consistent in all units in the region and is shown in Fig. 72.3.

Extracorporeal life support (ECLS) was used infrequently in patients with ALI as previously there was but one referral center in Australia (Victoria) and New Zealand (Auckland). Notably, endogenous surfactant was not used in patients with ALI.

72.3 Transport Services

Retrieval services are variable throughout Australia and New Zealand for neonates and children requiring mechanical ventilation. The demographics of Australia and New Zealand, with small populations spread over huge areas, make safe transport of neonates and children requiring mechanical ventilation a crucial issue. Traditionally, in Australia, retrieval of sick children was the preserve of the Royal Flying Doctor service, and while this service still operates in parts of Australia, more specialized transport services for neonates and children have been developed. These services are provided from central locations with medical and nursing staff

experienced in management of critically ill neonates and children.

There are many good examples of effective transport services in Australia and New Zealand. Some services transport both neonates and children (NETS in NSW), while others transport just neonates (NETS in Western Australia) or children (PETS in Victoria).

The benefits of employing more specialized staff is that the critical care unit can in some ways be delivered to the patient. In this way, neonates and children who are critically ill and require specialized support, such as mechanical ventilation, can receive this support as soon as the retrieval team arrives and can be stabilized prior to transfer to a tertiary center.

In Australian remote areas, there is an increased need for mechanical ventilation in patients from indigenous communities, who are overrepresented in ICU. Poor living conditions and inadequate medical services contribute to an increased incidence of respiratory disease as well as increased need for ventilation for other causes, particularly trauma. These children are particularly disadvantaged by living in remote areas and mortality rates are higher, in part because of isolation from tertiary medical services.

72.3.1 Neonatal Retrieval Services

Of all babies admitted to level III neonatal units, 23.3 % were transferred after birth. Of these, 80 %

(1,410) babies were transferred by specialist retrieval teams (Australian and New Zealand Neonatal Network 2006). Each state in Australia (apart from Tasmania) has its own retrieval service based in each capital city. These are usually based at one of the maternal or pediatric hospitals and include NETS (WA), SANETS (South Australia), NETS (NSW), PETS (Victoria), and QNETS (Queensland). Babies who are born outside the tertiary maternal hospitals are transferred by these specialist retrieval teams. The states (Tasmania) and territories (NT, ACT) with smaller populations have less well-resourced arrangements with both the RFDS (NT) and PETS (Victoria) assisting in these areas. These specialized teams usually comprise of an experienced nurse and neonatal trainee or specialist medical staff who are able to initiate mechanical ventilation and transfer these babies in a more stable condition.

In New Zealand, in some ways, a very similar arrangement is in place with neonatal retrieval services based in the major cities. Hence, each region is covered for retrievals. Babies requiring cardiac surgery are transferred to the single cardiac center (Auckland) by the respective transport service.

72.3.2 Pediatric Retrieval Services

Pediatric retrieval services are not as well developed as neonatal retrieval services in the region. While there are some good examples such as NETS (NSW) and PETS (Victoria), transport of ventilated, critically ill children is more ad hoc in Western Australia, where most transports from regional areas are performed by the Royal Flying Doctor Service (RFDS). While RFDS staff are trained in medical transport, they often have more limited specialized training or experience in pediatrics. In South Australia, pediatric transfers are controlled by the PICU, and PICU staff perform transfers.

While undoubtedly a well-funded operation with specialized staff (e.g., NETS in NSW) is the most efficient system, the enormous distances and sparse population in other areas in Australia and New Zealand limit the cost-effectiveness of

such well-organized systems. In Queensland, QNETS has recently been disbanded because of funding issues, thus shifting the burden of pediatric transfers directly onto PICU staff.

72.4 Role Delineation of Mechanical Ventilation in Pediatric Intensive Care

72.4.1 Initiation of Ventilation in Pediatric Intensive Care in Australia and New Zealand Is Based Upon Medical Decision Making

Patients referred to the tertiary centers are reviewed by an emergency specialist or intensivist, and decisions are made based on patient needs. For those patients based in regional areas, the decision to ventilate is made by the local doctor, usually in conjunction with the transport service and tertiary center, or by the transport teams themselves after they review the patient. Patients are almost always intubated by medical staff with assistance from nursing or other medical staff in pediatric ICU, whereas there is a greater input from nurses in the NICU, particularly in long-term patients.

72.4.2 Maintenance of Ventilation

As there are no respiratory therapists in Australia and New Zealand, mechanical ventilation is largely controlled by medical staff in intensive care. Decisions regarding which mode of ventilation, which type of ventilator, and which parameters are made by junior or senior medical staff attending the patient. Highly trained ICU nursing staff are essential in documenting ventilation parameters, documenting patient observations, and reacting to any rapid changes in patient condition. In many units, nurses are given some flexibility to change ventilatory parameters (especially FiO_2) in order to keep patient stable.

72.4.3 Weaning

While weaning protocols have been trialed and are still used infrequently by ICUs in the region, most weaning is not protocol driven. The degree of nurse-led weaning varies from unit to unit, but in all units, nurses play an essential role in monitoring weaning.

The dichotomy between ventilation practices in Australia/New Zealand and North America is most obvious when the role of the respiratory therapist is considered. In North America, maintenance of ventilatory parameters and weaning is guided (with varying degrees of medical supervision) by respiratory therapists who are trained specifically in the use of mechanical ventilation. There are many benefits to this system, but to some degree, this does result in some loss of skills by the medical staff in the intricacies of mechanical ventilation.

In Australia and New Zealand, the maintenance and weaning of ventilation has been the responsibility of medical staff with varying input from nursing staff. While this means that medical staff are required to supervise progress of ventilation, it does add to the workload of medical and nursing staff and may detract from their other responsibilities in patient care. While of course there will be proponents for both systems, in actual fact, both systems work well.

The role of the physiotherapist in intensive care in the region also varies. Physiotherapists have a central role, attending ward rounds and X-ray rounds in some units, while playing a more peripheral consulting role in others. While assisting the management of patients undergoing mechanical ventilation, physiotherapists have no role in the management of mechanical ventilation.

72.5 Monitoring of Mechanically Ventilated Patients

Monitoring of patients in intensive care is similar throughout Australia and New Zealand and is based on guidelines established by the Joint Faculty of Intensive Care Medicine in the monitoring of critically ill patients undergoing transport (2003). The recommended monitoring for ventilated children includes 1:1 nursing, percutaneous

oxygen saturation, and end-tidal CO₂ monitoring. All tertiary PICUs in Australia and New Zealand generally fulfil these guidelines. As well, all approved ventilators have a disconnect alarm.

The use of end-tidal CO₂ monitoring is much less frequent in neonatal units, but other modalities of monitoring, such as transcutaneous pO₂ and pCO₂, are more frequently used.

72.6 Positive Aspects of System

The system in place in Australia and New Zealand has many positive aspects. Mechanical ventilation is well centralized, and in general, efficient transport systems allow transfer of most patients to tertiary centers when necessary. This is particularly true in the major centers. Due to geography, many communities in both Australia and New Zealand are isolated with marginal medical facilities and infrastructure. These communities are significantly disadvantaged in the management of respiratory disease and in particular the management of children with respiratory failure. Due to the extreme isolation of these communities, however, it is difficult to envisage an efficient system.

As well as care being highly centralized, communication between tertiary units and those referring to it is good.

Transport systems are either run by the tertiary centers they refer to (Victoria, South Australia, Queensland) or communicate closely (NETS, NSW). In some areas (Western Australia), pediatric patients are less well catered for with the Royal Flying Doctor providing the bulk of prehospital transports.

The Australia and New Zealand Pediatric Intensive Care Registry collects data for almost all intensive care units caring for children (currently 22 units) and assesses performance of these units using validated mortality scoring systems.

72.7 Problems with System

Isolation and distance is the main problem with systems providing mechanical ventilation in children and neonates in Australia and New Zealand. A relatively small population (24 million) spread over

large distances makes it difficult to provide services, both in pediatric and obstetric/neonatal medicine.

Combined research in the area of mechanical ventilation has also been lacking in Australia/New Zealand with collaboration becoming more common over the past decade or so.

Conclusion

While relative economic prosperity provides a high standard of centralized care for neonates and children requiring mechanical ventilation in Australia and New Zealand, the unique geography and demographics of Australia and New Zealand provides many difficulties. In particular, neonates and children in remote areas are disadvantaged by delayed access to mechanical ventilation. While mechanical ventilation practices do not differ significantly from those in North America and Europe, the absence of respiratory therapists in Australia and New Zealand means that the initiation, control, and weaning of mechanical ventilation are mainly the prerogative of medical staff with assistance from specialized nursing staff.

Essential to Remember

Mechanical ventilation management is different from a country to another. This is a challenge to knowledge transfer in this field.

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Part XXIX

Ethical Concerns

Jeffrey Burns and Niranjan “Tex” Kissoon

Educational Aims

- To describe the variations in practices related to withholding or withdrawal of mechanical ventilation in pediatric and neonatal intensive care units across the world
- To discuss the special considerations in resource-constrained developing world
- To explore the parental perspectives with regard to withholding or withdrawal of mechanical ventilation
- To dwell on the special considerations in case of end-of-life situation in neonates
- To draw out a guideline for the withdrawal of mechanical ventilation at the end of life

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In 1929, Drinker and Shaw reported the first application of mechanical ventilation to a child in a hospital setting. The patient was an 8-year-old girl with “intercostal paralysis from poliomyelitis” who “was in the machine almost continuously for a total of 122 h, at the end of which time death occurred, resulting from cardiac failure brought on by an extensive bronchopneumonia in the right lung” (Drinker and Shaw 1929).

From that time until present, few areas of intensive care medicine have occupied the field as much as the study of how to use mechanical ventilation wisely. Few would argue that practitioners of intensive care medicine must be competent with the indications of mechanical ventilation as well as the ethical and practical aspects of when it is no longer indicated (Truog et al. 2001). Yet, determining when mechanical ventilation is, and is not, indicated raises many profound ethical, religious, moral, cultural, and legal questions in all ICUs across the world. Cultural and ethnic variations in attitudes and practices around decisions to withhold or withdraw mechanical ventilation from a critically ill infant or child are perhaps expected between continents, but key differences also exist on a more local basis within continents and within countries. Physicians need to be aware of these potential differences in the attitudes not only of their colleagues but also of their patients and families. The aim of this chapter is to provide a practical overview and update on many of these concerns.

Table 73.1 Observational studies of the frequency of the withholding or withdrawal of some form of life-sustaining treatment prior to death in the pediatric intensive care unit: 2000–2009 (Burns et al. 2000; Devictor and Nguyen 2001, 2004; Garros 2003; Kipper et al. 2005; Lago et al. 2005, 2008; McCallum et al. 2000; Moore et al. 2008; Stark et al. 2008; Tagarro Garcia et al. 2008; Tonelli et al. 2005)

First author (reference)	Tagarro Garcia	Stark	Lago	Moore	Lago	Kipper
Date	2008	2008	2008	2008	2005	2005
Location	Barcelona, Spain	Melbourne, Australia	Brazil	Westmead, Australia	Southern Brazil	Southern Brazil
#PICUs studied	1	1	7	1	3	3
Frequency (%)	5/26 (20 %)	42/50 (84 %)	186/428 (43 %)	20/27 (74 %)	56/155 (36 %)	92/575 (18 %)

First author (reference)	Tonelli	Devictor	Garros	Devictor	McCallum	Burns
Date	2005	2004	2003	2001	2000	2000
Location	Belo Horizonte, Brazil	Europe	Toronto, Canada	France	Edmonton, Canada	Boston, United States
#PICUs studied	1	39	1	33	1	3
Frequency (%)	59/112 (52 %)	116/350 (33 %)	72/99 (73 %)	106/264 (40 %)	59/97 (83 %)	53/100 (53 %)

73.1 Observational Studies on the Withholding or Withdrawal of Mechanical Ventilation: Striking Variability and Some Emerging Trends

Making decisions about end-of-life care is a frequent event in pediatric and neonatal intensive care, yet the conceptual foundation of the decision-making process remains heterogeneous. For example, there is large, growing, and consistent body of literature demonstrating high degree of variability throughout the world, both between individuals and between regions and continents, in how mechanical ventilation is utilized in end-of-life care (Hardart et al. 2002; Rebagliato et al. 2000; Sprung et al. 2003). Rather than objective variables, such as the severity of the illness and organ dysfunction, nearly all studies that have examined individual decision making on whether to withhold or withdraw mechanical ventilation reveal that the strongest determinants of the decision are typically personal characteristics of the physician or parent making the decision (Randolph et al. 1999; Cook et al. 2003, 2006). Nearly all studies that have examined outcomes of decisions to limit life-sustaining treatments in children at a regional or national level have found a striking north-south divide in how these

decisions are made. Broadly stated, and as seen in Table 73.1, with the exception of practice in Australia, observational studies in the southern hemispheres, and the southern portions of continents in the northern hemisphere, reveal that withholding or withdrawal of mechanical ventilation from critically ill infants, children, or adults is practiced less frequently. Similar observational studies in the northern hemisphere, and in Australia and the northern portions of continents in the southern hemisphere, reveal end-of-life practices that are more often associated with a decision to withhold or withdraw mechanical ventilation from critically ill infants, children, or adults (Sprung et al. 2003; Cohen et al. 2005; Devictor et al. 2008; Kapadia et al. 2005; Lago et al. 2007; Levin and Sprung 2003; Salahuddin et al. 2008; Sprung et al. 2007; Vincent 2001; Yaguchi et al. 2005). Relatively smaller data is available from the neonatal units. Table 73.2 shows that the end-of-life decisions in NICUs across the world including that from a less developed country were almost similar.

It is not clear why differences in end-of-life decision making for infants and children in similar circumstances, except for their place of residence, exist. As with other intensive care practices, the goal should be to identify and implement best practices. However, objective data to guide these

Table 73.2 Observational studies of the frequency of the withholding or withdrawal of some form of life-sustaining treatment prior to death in the neonatal intensive care unit (Verhagen et al. 2007; Vrakking et al. 2005; Wong and Lam 2004; Roy et al. 2004; Singh et al. 2004; Cuttini et al. 2000; Van der Heide et al. 1997; Wall and Partridge 1997; Ryan et al. 1993)

First author	Verhagen	Vrakking ^a	Wong	Roy	Singh
Year	2007	2005	2004	2004	2004
Place	Venezuela	The Netherlands	Hong Kong	United Kingdom	USA
Frequency (%)	24/32 (75 %)	154/233 (68 %)	28/40 (70 %)	41/71 (58 %)	50 %
First author	Cuttini ^b	Van der Heide ^a	Wall	Ryan	
Year	2000	1997	1997	1990–1991	
Place	Europe	The Netherlands	USA	Alberta, Canada	
Frequency (%)	46–90 %	184/299 (62 %)	121/165 (74 %)	80 %	

^aCombined data for all infants <1 year of age

^bPhysician survey of 122 NICUs in seven countries of Europe

decisions, such as predictive models of who will survive mechanical ventilation, or survive without severe and permanent injury, remain poorly developed. Indeed observational studies suggest that ICU physicians discriminate between survivors and non-survivors more accurately than do scoring systems in the first 24 h of ICU admission, implying limited usefulness of outcome prediction in the first 24 h for clinical decision making (Sinuff et al. 2006). Moreover, end-of-life care differs from most other medical problems, in that best practice not only is defined in terms of evidence-based strategies but also relates to prevailing cultural, religious, and legal norms (Cook et al. 2006; Truog 2005).

A decision-making process about the withholding or withdrawal of mechanical ventilation for infants and children at the end of life that meets the approval of all cultures across the world is unlikely. Yet, most would likely see a decision-making process about end-of-life care that always leads to only one conclusion as harmful. For example, a process that always advocates for the withholding or withdrawal of life-sustaining treatment for critically ill infants or children would rightfully be seen as harmful and flawed for failing to recognize instances where providing ongoing treatment was in the child's best interests. Similarly, a process that never allowed for the withholding or withdrawal of life-sustaining treatment for critically ill children would also be seen as harmful and flawed for failing to recognize instances where biologic

existence supported by medical technology may be technically possible but may not be in the infant or child's best interests. The healthcare personnel involved in non-initiation and withdrawal of care may also be concerned about lack of or limitations of legal provisions to protect them. The laws related to withdrawal of care are not uniform across nations and often nonexistent in many countries (Rao 2005). The decisions about withdrawal or non-initiation should consider the best available and recent data for the outcomes of the disease with the available type of medical care in the given circumstances. Understandably as the quality of medical care improves, the outcomes may change. For example, traditionally, babies who develop severe IVH have been believed to have high mortality and high incidence of sequelae in survivors. Recent studies have, however, shown a decrease in mortality from severe IVH to 30–40 % and markedly improved quality of life in survivors (Bassan and du Plessis 2008; Bassan et al. 2007; Roze et al. 2008). Hence, a decision to actively withdraw support from a hemodynamically stable premature infant with severe IVH may be difficult to justify ethically in centers with good quality medical care. Withdrawing ventilator assistance also involves consideration of stopping other treatments. Caregivers and family may feel greater dilemmas with regard to withholding feeds and fluids than the withdrawal of mechanical ventilation. In the developed world, withholding medical fluids and food may be



Fig. 73.1 The incidence of withholding or withdrawal of mechanical ventilation at the end of life increases with practice in more northern and western locations across the world

morally more acceptable (Porta and Frader 2007). The American Academy of Neurology sanctions the withdrawal of nutrition and fluids in persistent vegetative states if agreed by their care providers and parents (Position of the American Academy of Neurology on certain aspects of care and management of persistent vegetative state patient 1989). In the Eastern cultures, however, the families are more likely to be inclined to continue food and water even by artificial means. Giving food and water to the hungry and thirsty is considered a great act of compassion, while starving a dependent person is abhorred (Singh 2007). However, all will agree that aggressive nutritional interventions like parenteral nutrition can be withdrawn (Carter and Leuthner 2003) (Fig. 73.1).

To address the need for a framework to guide the decision-making process, a growing number of national professional societies have issued guidelines around decisions to forego life-sustaining treatment for critically ill infants and children (American Academy of Pediatrics Committee on Bioethics 1994; Aita et al. 2008; Bulow et al. 2008; Cabre et al. 2008; Cremer

et al. 2007; Hubert et al. 2005; Mani 2006; Pedersen et al. 2007; Tibballs 2006; Truog et al. 2005; Waisel et al. 2002; Zamboni 2002).

73.2 Special Considerations in the Developing World

Many developing and underdeveloped countries of Asia and Africa have limited financial resources devoted to healthcare, combined with burgeoning populations. As a result the number of PICU and NICU beds and ventilators is very limited compared to the needs. In addition, the healthcare systems are different with most of the expenditure of initial hospital care as well as for follow-up rehabilitative services being borne by the families. The health insurance is either non-existent or grossly underdeveloped. The social systems and rehabilitative services required to take care of children of different abilities and handicaps are virtually not there. The education and information level of the parents are often low. There may even be gender bias against female infant in some cultures. On the other

hand, people's faith and belief in the abilities of healthcare providers is enormous, and decision making is often left on them. The physicians may also face difficulty because of lack of objective outcomes data from their own setups.

In view of the above, complex socioeconomic realities often outweigh ethical considerations (Miljeteig et al. 2009). Policies of prioritization are followed for hooking sick children or neonates to the ventilator. Priority is given to children having potentially salvageable disorders and neonates above 1,000 g. The situation, however, becomes even more difficult leading to a lot of mental turmoil and dilemmas, when a child or neonate in a vegetative state or with an expected poor long-term outcome is already occupying a ventilator and there is another salvageable child or infant with potentially much better prognosis needing the ventilator.

73.3 Parental Perspectives on End-of-Life Care: Communication Must Improve

The death of a child is perhaps the worst tragedy a family has to ever endure. For many of these parents, their child's final days were dominated by the question: Is it appropriate to continue life-sustaining therapy? Decisions of such import are emotionally stressful and are often a source of disagreement, but until recently only informal understanding of the parent's experience was reported. The past decade has seen increasing literature on parental perspectives to improve the quality of end-of-life care and communication.

The consistent finding of this literature is that bereaved parents report problems related to optimal communication as one of the major deficiencies in the end-of-life care provided to their child (Widger and Picot 2008). Consistent and effective communication from one level of care and one set of providers to the next is a basic expectation, but is usually not met. Meyer and colleagues conducted a study of 56 bereaved parents of children cared for at three PICUs in the USA and found that parents identified six priorities for

pediatric end-of-life care including honest and complete information, ready access to staff, communication and care coordination, emotional expression and support by staff, preservation of the integrity of the parent-child relationship, and faith (Meyer et al. 2006). More recently, Meert and colleagues reported on the experience of the bereaved parents of 48 children cared for at six PICUs in the USA. These investigators found that the most common communication issue identified by parents was the physicians' availability and attentiveness to their informational needs. Other communication issues included honesty and comprehensiveness of information, affect with which information was provided, withholding of information, provision of false hope, complexity of vocabulary, pace of providing information, contradictory information, and physicians' body language (Meert et al. 2008).

Parents' views of the adequacy of pain management, decision making, and social support during and after the death of their child were also measured through a self-administered questionnaire survey of 56 bereaved parents by Meyer and colleagues. In 90 % of cases, physicians initiated discussion of withdrawal of life support, although nearly half of parents had considered it independently. Among decision-making factors, parents rated the quality of life, likelihood of improvement, and perception of their child's pain as most important. Twenty percent of parents disagreed that their children were comfortable in their final days. Fifty-five percent of parents felt that they had little to no control during their child's final days, and nearly a quarter reported that, if able, they would have made decisions differently. There were significant differences between the involvement of family, friends, and staff members at the time of death and greater agreement about the decision to withdraw support between parents and staff members than with other family members. These investigators concluded that parents place the highest priorities on quality of life, likelihood of improvement, and perception of their child's pain when considering withdrawal of life support. Parents make such decisions and garner psychosocial support in the context of a social network that changes over

time and includes healthcare professionals, family, and friends (Meyer et al. 2002).

More important than the actual outcome, recent data also suggests that many parents want more involvement in end-of-life planning, from discussions around the location of death to even consideration of a plan for extubation at home. These data suggest that it is very important to provide additional choices for parents wishing to maximize end-of-life quality outside the hospital setting (Dussel et al. 2009; Zwerdling et al. 2006).

Bereaved parents often desire a physician-parent conference after their child's death in the pediatric intensive care unit. Meert and colleagues analyzed the audio-recorded telephone interviews from 56 bereaved parents regarding the communication provided around the end of life for 48 children in six PICUs in the USA. In this study, only seven (13 %) parents had a scheduled meeting with any physician to discuss their child's death; 33 (59 %) wanted to meet with their child's intensive care physician. Of these, 27 (82 %) were willing to return to the hospital to meet. Topics that parents wanted to discuss included the chronology of events leading to PICU admission and death, cause of death, treatment, autopsy, genetic risk, medical documents, withdrawal of life support, ways to help others, bereavement support, and what to tell family. Parents sought reassurance and the opportunity to voice complaints and express gratitude (Meert et al. 2007).

In sum, the potential for strained communications is mitigated if clinicians provide timely clinical and prognostic information and support the family with a comfortable setting and continuous psychosocial support. Effective communication includes sharing the burden of decision making with family members.

73.4 Special Considerations for Neonates

The situation of non-initiation or withdrawal of care in the newborn may arise because of major malformations, severe perinatal asphyxia, massive intracranial hemorrhage, or extreme prematurity. The cutoff for extreme prematurity varies

from <24 weeks in the most developed world to <28 weeks in the developing world. The decision making is more objective if local outcomes data based on the available resources and expertise is used for prognostication. The families may have developed lesser attachment to the newborn compared to the older child, hence may be more agreeable for withdrawal of care if the situation demands, without harboring long-term guilt feelings.

A special situation in the newborn is severe birth asphyxia needing prolonged resuscitation, which is often unanticipated and in which very little time is available for investigations and consultations. The concern is not only whether resuscitation will be successful, but also whether if successful, the infant will have an intact survival. The situation is more difficult in developing countries where the brain-damaged infants may be considered a burden to the family and the society because of limited financial and healthcare resources (Ho 2001).

73.5 A Guideline for the Withdrawal of Mechanical Ventilation at the End of Life: Anticipating and Coordinating Care

The withdrawal of mechanical ventilation with the intention of allowing an infant or child to die raises difficult and rapidly evolving clinical and ethical decision making more profoundly than any other context. While the withdrawal of any life-sustaining treatment potentially raises the same issues, the abrupt and unpredictable change in patient symptoms is especially pronounced as assisted ventilation is withdrawn. Failure of the clinical team to anticipate many different possible patient responses to the cessation of assisted ventilation, and make the parents aware of this and have in place a flexible and effective plan of care to address changes as they arise, can lead to abrupt decisions that leave both the patient's parents, nurses, and clinicians with lasting emotional distress. Given this context, how can clinicians provide care that effectively responds to the

evolving physiologic, emotional, and spiritual needs of the patient and their family members in a timely manner and within an ethical framework consistent with the values of the medical profession and society in which we live?

What is the most compassionate means of withdrawing mechanical ventilation with the intention of allowing the patient to die? How should signs of apparent patient suffering be treated after the ventilator is removed? The abrupt onset of respiratory distress as mechanical ventilation is withdrawn, coupled with the uncertainty on how effectively and how long the patient may be able to breathe without mechanical ventilation, makes dosing medications for symptom relief especially difficult for clinicians. What is the clinical and ethical goal in using sedatives and analgesics in this context? Administering too much sedation is likely to compromise effective respirations even further and thus hasten death, while too little sedation will abandon a dying patient to untreated suffering; therefore, are the goals of care in this context inevitably contradictory and ambiguous? What should one do if the family thinks the patient is suffering and requests more sedation but the clinicians assess the patient to have no apparent discomfort? A practical guideline, based on the Society of Critical Care Guidelines (Truog et al. 2001) and adapted from the protocol used at Boston Children's Hospital, outlines eight steps:

Prior to the withholding or withdrawal of life-sustaining treatments, the attending physician, bedside nurse, and other physicians, nurses, therapists, and medical students, and preferably including other members of the clinical team such as clergy and psychosocial experts, should huddle. The clinicians should openly discuss and review the following principles:

1. What treatments may be withheld or withdrawn?
 - It is ethical and legal to withhold or withdraw any medical treatment when the patient's family, as informed by a recommendation from the attending physician, determines that the burdens of such treatments outweigh the benefits.
 - Any medical intervention, from ECMO and pacemakers to the use of physiologic

monitors, may be withheld or withdrawn from the dying patient in the ICU.

- We *never* withdraw *care*, only treatments and interventions.
 - A guiding concept in determining what treatments to continue and what treatments to withhold or withdraw is that any intervention that appears to promote the patient's comfort or dignity (as well as ameliorate emotional, psychological, or spiritual concerns) should be continued. Those that do not appear to promote the patient's comfort or dignity should be withdrawn.
2. How should mechanical ventilation be withdrawn?
 - An artificial airway may be removed (extubation), or the patient may have supplemental oxygen and/or positive pressure ventilation gradually reduced (terminal wean with no plan for extubation). The method of withdrawal should be guided by the specific circumstances of the patient.
 - A patient likely to experience significant hemoptysis, for example, may benefit from a terminal wean with the gradual reduction in FiO_2 and/or ventilator rate at a pace not faster than pharmacologic sedation is administered to treat objective signs of distress from the effects of hypoventilation and hypoxia.
 - Studies suggest that the most rapid descent into unconsciousness with the least agitation occurs when hypoxia is allowed to progress in the face of normocarbia.
 - Many parents will request that mechanical ventilation be withdrawn by having their child extubated. In this case, the abrupt removal of respiratory support will likely lead to the abrupt escalation in symptoms of respiratory distress. In this case the patient generally should receive sedation or analgesia prior to extubation in anticipation of respiratory distress, with subsequent doses titrated to the patient's level of discomfort.
 - It is not a violation of the medical examiner policies to withdraw the endotracheal tube as the means of withdrawing life-sustaining treatment in the ICU at the request of informed and responsible parents.

3. How should signs of apparent discomfort be treated?

- Treatment of discomfort may include pharmacologic and nonpharmacologic strategies. Palliative measures should be comprehensive and not rely solely on sedation and analgesia. For example, simple positioning or massage may be effective.
- Assessment of breathing patterns can be complicated in dying patients. Irregular breathing patterns are a natural part of dying and may not be uncomfortable for the patient. Unfortunately, the irregular pattern that accompanies dying is often referred to as “agonal,” which may imply to the family and other clinicians that the patient is in “agony.”
- Gasping is a medullary reflex and can occur in the absence of consciousness. Similarly, noisy respirations from airway secretions (the “death rattle”) are more likely to be distressing to the family and other observers than they are to the patient. All gasping does not need to be treated with escalating doses of sedatives or narcotics, ideally the decision should be made on a consensus between the family and clinicians at the bedside on whether the patient activity appears to be causing, or is a manifestation of, suffering.
- In general, the clinician’s obligation is to treat objective signs of discomfort as experienced by the patient. The distress of the family should be addressed by continued reassurance and emotional support.

4. Neuromuscular blockade and the withdrawal of mechanical ventilation

- Neuromuscular blocking agents (NMBAs) have no sedative or analgesic properties and may mask symptoms of suffering at the end of life. As a general rule, therefore, pharmacologic paralysis should be avoided at the end of life.
- In most cases, the effect of these agents can be reversed or allowed to wear off within a short period of time, allowing for the withdrawal of mechanical ventilation in the absence of the confounding effects of

paralysis. Patients who have been receiving NMBAs chronically for management of their ventilatory failure occasionally can present a more difficult ethical dilemma. In some situations, restoration of neuromuscular function may not be possible for several days or even weeks. When faced with this problem, the clinician must choose between withdrawal of the ventilator while the patient is paralyzed and continuation of life support well beyond the point at which the physician and family have determined that the burdens of such treatments outweigh the probable benefits. In this circumstance, it may be preferable to proceed with withdrawal of life support despite the continued presence of neuromuscular blockade.

5. How much is too much sedation and analgesia?

- Current ethical and legal guidelines place importance on the intentions of clinicians in administering analgesics and sedatives at the end of life. Specifically, clinicians should administer doses that *are intended to relieve pain and suffering but not intended to directly cause death*. We cannot, however, give more sedation than what the patient needs to be comfortable (be prepared for the request, “Please, can’t we just get over with this”).
- Because intentions are essentially subjective and private, the only ways to infer the nature of a clinician’s intentions are by self-report and by an analysis of his or her actions. Accordingly, documentation of one’s intentions in the patient’s chart is an important part of providing end-of-life care. When “p.r.n.” orders are written for analgesics and sedatives, the indication for administration should be stated clearly (e.g., pain, severe upper airway obstruction). This reduces the likelihood of misinterpretation or abuse.
- For example, when a clinician titrates morphine in doses of 1, 5, or 10 mg every 10 or 20 min, it is plausible to conclude that the clinician intends to make the patient comfortable and not to directly cause the patient’s death. On the other hand, when a

clinician administers 2,000 mg of morphine acutely to a patient who is not profoundly tolerant, it raises concern that the clinician may have primarily intended to cause the death of the patient.

- Sedation and/or analgesia should be titrated to effect, and the dose should not be limited solely on the basis of “recommended” or “suggested” maximal doses. In most cases, patients who do not respond to a given dose of an opioid or benzodiazepine will respond if the dose is increased—there is no theoretical or practical maximal dose.
 - The concept of “anticipatory dosing” (as opposed to reactive dosing) also should guide clinicians in the use of sedation and analgesia at the end of life. The rapid withdrawal of mechanical ventilation is an example of the need for anticipatory dosing. At the time of ventilator withdrawal, the clinician can anticipate that there will be a sudden increase in dyspnea. It is not sufficient simply to respond to this distress with titrated doses of an opioid (reactive dosing). Rather, clinicians should anticipate that the abrupt withdrawal of assisted breathing will trigger increased respiratory distress and therefore they should provide adequate sedation or analgesia beforehand (anticipatory dosing). As a general rule, the doses of medication that the patient has been receiving hourly should be increased by two- or threefold and administered just before withdrawing mechanical ventilation.
6. What is the goal in using sedatives and analgesics in this context?
- The goal of titrating sedatives and analgesics after withdrawal of mechanical ventilation is only to treat objective signs of discomfort that evolve; it is not to bring about a certain outcome. Stated another way, the target is to make the patient comfortable, the target is not some arbitrary maximum dose, and the target is not the death of the patient.
 - If there are no objective signs of discomfort and the patient breathes effectively after extubation, despite our prediction that death would immediately follow withdrawal of ventilation, there should be no panic among the clinicians that something is wrong and further sedatives or analgesics must be administered. If the patient is unexpectedly breathing comfortably after extubation, continue all other non-medication measures of palliative care and provide ongoing and comprehensive support for the family.
7. What basic documentation is essential?
- On the other hand, it may take multiple boluses of escalating doses of sedatives and analgesics to treat clear signs of discomfort after extubation in order to keep the patient comfortable.
 - Either way, our frame of mind before the withdrawal of life-sustaining treatments is that we accept that patient’s will proceed at their own time and pace. We respond to what evolves, but it is not our intention in administering sedatives and analgesics to ensure that a certain outcome evolves.
 - Our sole focus is only that a patient for whom life-sustaining treatments have been withheld or withdrawn not be left with untreated, objective, signs of suffering.
 - A brief description must be placed in the patient’s medical record of the decision-making process that led to the withholding or withdrawal of life-sustaining treatment and the palliative care provided.
 - For example, when describing the decision-making process, one should note the date and time of the family meeting, those present, and some statement that conveys that there is “agreement between the family members and the clinician team that the burdens of life-sustaining treatments outweigh any remaining benefit and that the decision has been made to withdraw life-sustaining treatments at this time.” If a decision of do not resuscitate (DNR) is made, it must be explicitly documented what all will be done and what all is not to be done in the event of an acute deterioration.
 - In describing the palliative care measures provided, it is important to briefly document

the rationale used to titrate sedation and analgesia, if administered. For example, “Signs of suffering were noted with the onset of gasping respirations and increased work of breathing after the patient was extubated. Morphine and Versed were ordered by Dr. Burns and administered by L. Pixley, RN, and titrated to treat these signs of patient suffering. The patient’s signs of suffering were relieved after three boluses over 20 minutes and the patient expired at 9:00 AM.”

8. Preparation of the family

- A huddle with the family after the clinical team meeting is essential in guiding them on what to expect and may alleviate some of their anxiety around the process.
- After the clinician huddle, preferably the senior physician and bedside nurse should huddle with the family to provide clear and explicit explanations about the process of withdrawal of life-sustaining treatments and assurance that symptoms of patient suffering will be treated (providing a brief and compassionately worded overview of the principles of care to be followed, as outlined in #1–7 above).
- Avoid making firm predictions about the patient’s clinical course after withdrawal of mechanical ventilation or other forms of life-sustaining treatment as they are often inaccurate and may result in a substantial loss of credibility when predictions about death or the timing of death are in error. In answer to questions about what will happen, it is better to say, for example, “We think it is unlikely that your son will survive after the ventilator is withdrawn, but whether he breathes only for a short time or for a very long time, we can assure you that we will treat symptoms that appear to be causing him discomfort.”
- At times it will be necessary for the clinicians to anticipate, ask, and answer questions that the family appears to be afraid or unable to verbalize. “Sometimes after the ventilator is withdrawn, patient’s experience a change in skin color, or unusual

breathing noises, and this is to be expected and our job is make sure that your child does not experience symptoms of suffering or discomfort. If we see signs of discomfort, we will treat them.”

- Families should have the opportunity to be helpful and invited to participate in activities to relieve discomfort, such as mouth care, bathing, and repositioning. They should be encouraged to participate in assessment of the patient’s pain and suffering, and they should be encouraged to provide other means of comfort to the patient that were important to them before, such as holding or rocking their child, wrapping the child in a special blanket and giving their child a massage).
- The religious faith and wishes of the family with regard to any prayer sessions and harmless rituals should be respected.

Future Perspectives

With the exponential advances in medical technology, our ability to sustain life “artificially” is going to increase more and more. This is going to raise hugely complex ethical questions related to the “beginning” and “end” of life. The issue will be further compounded by the rapid strides in information and communication technology by which options and experiences can be shared quickly and easily. There is an urgent need to anticipate and conduct more intensive research into the ethical issues related to end-of-life care.

Essentials to Remember

- There is a huge variability in the practices related to withholding or withdrawal of mechanical ventilation across the globe; the prevalence of withdrawal of care seems to be more common in northern hemispheres, Australia, and northern parts of southern hemispheres

- The decisions about non-initiation or withdrawal should consider the best available and recent data for the outcomes of the disease with the available type of medical care in the given circumstances. The outcomes would change over time with improvements in care, and hence the decisions would also evolve over time.
- In resource-constrained situations, socioeconomic realities often have to be balanced with ethical considerations.
- The decision-making and end-of-life process should involve effective, timely, honest, and comprehensive communication with the family. A clear but flexible plan should be made and documented about the what, how, and when of the withdrawal process, after discussions between the physicians, nurses, therapists, and other members of the clinical team and family.

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Index

A

- ABG. *See* Arterial blood gas (ABG)
- Absolute humidity, 276
- Acetaminophen, 1021
- Achondroplasia, NRS, 522, 523
- Acute chest syndrome, 574–575
- Acute hypoxic respiratory failure (AHRF)
 - clinical management, 1282–1285
 - in ECMO
 - complications, 1528–1529
 - indications and contraindications, 1528
 - outcome, 1529–1531
- Acute lung injury (ALI), 87–88
 - acute hypoxic respiratory failure management, 1282–1285
 - adjunctive therapy, 1285
 - AECC criteria, 1279
 - alveolar pathology during, 1280
 - alveolar recovery during, 1281
 - animal studies, 787–788
 - and ARDS, 1491
 - cell-mediated mechanisms, 1280
 - clinical outcomes, 1282
 - with concurrent brain injury, 574
 - definition, 1279
 - epidemiology, 1281
 - fluid management (*see* Fluid management, in pediatric patient)
 - general supportive care, 1285–1286
 - HFOV, 1284
 - human studies
 - benefits of exogenous surfactant therapy, 790–791
 - clinical outcomes, 792–793
 - combination therapy, 794
 - Exosurf®, 792
 - lung transplantation, 793
 - meconium, 790
 - pneumonia, 791
 - porcine surfactant, 792
 - post hoc analysis, 792–793
 - hypoxia, 1282
 - lung mechanics, 1281
 - management, 1286
 - mechanical ventilation failure, 1285
 - pathophysiology, 1279–1280
- PEEP, 1149–1151
 - prone position
 - check list, 681, 683–684
 - complications of, 680–681
 - contraindications for, 679–680
 - diseased lungs, 673–675
 - effectiveness and outcomes, 675–679
 - indications for, 679–680
 - long-term outcomes, 682
 - normal lungs, 672–673
 - principles, 671–672
 - risk factors, 1282
 - sepsis and, 1376
 - surfactant dysfunction, 785–786
 - ventilator-associated lung injury
 - definition of, 933
 - etiologies of, 934
 - prevention and management, 935–936
- Acute neonatal lung disease, 77
- Acute neonatal respiratory failure
 - apnoea of prematurity
 - afferent interactions, 1239–1240
 - breathing control, 1234–1235
 - central circuitry and output determinants, 1236–1237
 - central responses to blood gases, 1237–1238
 - definition and types, 1235–1236
 - homeostasis and limits, 1235
 - motor responses, 1238–1239
 - natural history/discharge/home monitoring, 1242–1243
 - presentation and differential diagnosis, 1239–1241
 - prognosis/follow-up, 1243
 - sinus arrhythmia and reflex bradycardia, 1238
 - therapy, 1239–1242
 - congenital diaphragmatic hernia
 - delivery room resuscitation and stabilization, 1226
 - epidemiology, 1225
 - extracorporeal membrane oxygenation, 1230–1231
 - intensive care management, 1226
 - outcomes, 1231–1232
 - pre- and postoperative ventilation, 1226–1227
 - pulmonary vascular management, 1228–1230
 - surgical repair and thoracic compliance, 1227–1228

Acute neonatal respiratory failure (*cont.*)

- definitions, 1185–1186
- infant respiratory distress syndrome
 - adjunctive therapies, 1203–1206
 - classical complications, 1206–1207
 - continuous positive airway pressure, 1192–1195
 - delivery room management, 1191–1192
 - epidemiology, 1189–1190
 - extracorporeal membrane oxygenation, 1202
 - general management, 1192
 - HFJV, 1202
 - HFOV, 1201–1202
 - humidified nasal cannula oxygen delivery, 1196–1197
 - incidence, 1190
 - INSURE technique, 1195–1196
 - lung mechanics, 1188–1189
 - nasal intermittent positive pressure ventilation, 1197–1199
 - partial liquid ventilation, 1202
 - pathophysiology, 1186–1188
 - risk factors, 1190–1191
 - short-and long-term outcomes, 1207–1208
 - supplemental oxygen, 1192
 - ventilation, 1199–1201
 - weaning, 1202–1203
- meconium aspiration syndrome
 - bolus surfactant therapy, 1222
 - complications, 1223
 - continuous positive airway pressure, 1219
 - conventional mechanical ventilation, 1220–1221
 - corticosteroid therapy, 1222
 - epidemiology, 1218
 - extracorporeal membrane oxygenation, 1222–1223
 - HFJV, 1221
 - HFOV, 1221
 - incidence, 1218
 - inhaled nitric oxide, 1222
 - intubation, 1219
 - lavage therapy, 1222
 - lung mechanics and functional residual capacity, 1216–1217
 - oxygen therapy, 1218–1219
 - pathophysiology, 1214–1217
 - risk factors, 1218
 - short-and long-term outcomes, 1224
- neonatal pneumonia
 - epidemiology, 1210
 - incidence, 1210–1211
 - lung mechanics, 1209–1210
 - pathophysiology, 1209
 - respiratory support, 1211–1213
 - risk factors, 1211
 - short-and long-term outcomes, 1213
- Acute respiratory distress syndrome (ARDS), 87–88, 736. *See also* Acute lung injury (ALI)
- CT imaging studies, 451, 452
- fluid management (*see* Fluid management, in pediatric patient)

HFOV

- in adult patients, 570–571
- in pediatric patients, 570
- timing of, 571–572
- PEEP impacts in, 1343–1347
- prone position (*see* Prone position, acute lung injury)
- and RSV, 1304–1305
- sepsis and, 1376
- ventilator-associated lung injury
 - definition of, 933
 - etiologies of, 934
 - prevention and management, 935–936
- Acute respiratory failure (ARF), NIV, 256
 - acute airway obstruction, 514, 515
 - acute pulmonary edema, 517, 518
 - bronchiolitis, 515
 - cardiogenic acute pulmonary edema, 518
 - clinical criteria, 513
 - nasal mask, 255, 257
 - nasogastric tube, 261
 - negative intrathoracic pressure, 518
 - neuromuscular diseases, 518
 - noninvasive ventilation, 513, 514, 516, 518, 519
 - oronasal masks, 255, 257
 - physiopathological classification of, 513, 514
- Acute severe asthma, 736
- Adjunctive therapies
 - heliox
 - intubated child, 1088
 - nebulisation source, 1088
 - noninvasive ventilation, 1088–1093
 - properties, 1086–1087
 - side effects, 1093
 - spontaneously breathing infant, 1087–1088
- MAS
 - bolus surfactant therapy, 1221
 - corticosteroid therapy, 1222
 - extracorporeal membrane oxygenation, 1222–1223
 - inhaled nitric oxide, 1222
 - lavage therapy, 1222
- in neonatal respiratory failure
 - antenatal steroids, 887–889
 - BPD, drugs for, 898–899
 - corticosteroids, 896–897
 - methylxanthines, 897–898
 - non-pharmacologic interventions, 900
 - patent ductus arteriosus closure, drugs for, 898
 - pulmonary vasodilators, 894–896
 - sedatives and analgesics, 899–900
 - surfactant replacement therapy, 889–894
- noninvasive respiratory support, 510–511
- in pediatric respiratory failure
 - heliox, 905–907
 - pulmonary vasodilators, 904–905
 - surfactant, 901–904
- RDS
 - analgesia, sedation and neuromuscular paralysis, 1206
 - antibiotics, 1205

- diuretics, 1205–1206
- exogenous surfactant, 1203–1205
- heliox, 1205
- inhaled nitric oxide, 1205
- methylxanthines, 1205
- Aerosolized antibiotics
 - recommendations, 853
 - therapy, 851–852
 - ventilated patients, 853
 - ventilator-associated pneumonia prevention, 852–853
- Aerosols
 - airway humidification, 279
 - drug delivery
 - advantages, 838
 - bronchodilators, 838
 - characteristic and behavior, aerosols, 839–841
 - humidification of inhaled gas, 846
 - infant vs. adult lung, 838
 - liposome encapsulation, 838
 - location, of generators, 845–846
 - metered-dose inhalers, 843–845
 - pneumatic nebulizers, 841–843
 - types of, 841
 - ventilator settings, 847
 - vibrating mesh nebulizers, 843
- Air leaks, detection of, 219
- Air leak syndromes
 - HFJV, 578–579, 1177–1178
 - HFOV, 573, 1166–1167
- Airway gas flow
 - laminar flow, 300
 - Reynolds number, 301–302
 - turbulent flow, 300–301
- Airway humidification
 - aerosol water particles, 279
 - heat and moisture exchangers, 278–279
 - heated humidifiers, 277–278
 - hygroscopic condenser humidifiers, 278–279
 - irrigation of airway, 279–280
 - physics of, 276–277
 - physiology of, 275
 - requirements, 280
 - water delivery options, 277
- Airway obstruction
 - flow-volume loops, 1151–1152
 - invasive conventional mechanical ventilation
 - lower, 547–548
 - upper, 536, 543–544
- Airway pressure release ventilation (APRV), 198, 1546
 - advantages of, 199
 - airway and circuit resistance, effects of, 202
 - application of, 200–201
 - contraindications and disadvantages, 202
 - definition of, 199
 - interference with spontaneous breathing, 202–203
 - parameters, 199
 - physiological effects of, 199–200
 - pressure-controlled ventilation, 202
 - transpulmonary pressure, decrease in, 202
 - weaning, 201–202
- Airway pressure relief (APR) valve, 1508
- Airway resistance, 296–297
 - measurement in constant-flow ventilation mode, 215–216
 - monitoring of, 212–216
 - patients with increased, 214
- Alfentanil, 1036
- ALI. *See* Acute lung injury (ALI)
- Alimemazine, 1044
- Alveolar dead space, 159
- Alveolarization, 10–11
- Alveolar ventilation, 396–397
 - HFOV, 1169
 - respiratory acidosis, 1146
 - respiratory alkalosis, 1146–1147
 - ventilatory requirements, 1145
- Alveologenesis. *See* Alveolarization
- Ambrisentan and sitaxentan, 827–828
- American-European Consensus Criteria (AECC), for ALI, 1279
- Analgesia. *See* Pain control, pediatric ICU
- Anatomical dead space, 159
- Anesthetic conserving device (ACD), 878–880
- Angiotensin-converting enzyme (ACE)
 - activity, 1286
 - inhibitor, 1286
 - VALI, 930, 931
- Animal-derived surfactants
 - bovine surfactant, 765
 - porcine surfactant, 766
 - prophylaxis, 770
 - vs. protein-containing synthetic surfactants, 777–778
 - vs. protein-free synthetic surfactants, 776–777
 - rescue therapy, 769–770
- Antenatal steroids
 - benefit of, 78
 - in neonatal respiratory failure, 887–889
 - RDS, 1189–1190
 - VALI, 923
- Anticholinergics, for asthma treatment, 1320
- Anti-inflammatory drugs
 - for BPD, 1273
 - for ventilator-associated lung injury, 925
- Apnoea
 - of prematurity
 - afferent interactions, 1239–1240
 - breathing control, 1234–1235
 - central circuitry and output determinants, 1236–1237
 - central responses to blood gases, 1237–1238
 - definition and types, 1235–1236
 - homeostasis and limits, 1235
 - motor responses, 1238–1239
 - natural history/discharge/home monitoring, 1242–1243
 - presentation and differential diagnosis, 1239–1241
 - prognosis/follow-up, 1243
 - sinus arrhythmia and reflex bradycardia, 1238
 - therapy, 1239–1242
 - test, 409–410, 1293

- Apoptosis and neurotoxicity, 1054–1055
- Arnold–Chiari syndrome, NRS, 521
- Arterial blood gas (ABG)
- measurement, 51
 - sampling, 552
- Arterial hypoxemia
- causes of, 537
 - treatment for, 1151
- Assist control ventilation (ACV), 164, 1425
- cycle time settings, 617–619
 - expected physiologic effects, 619–620
 - vs. IMV, 172
 - inspiratory flow settings, 616–617
 - in neonatal patient, 620–621
 - in pediatric patient, 621
 - principles, 616
 - weaning strategy, 165
- Assisted ventilation, 184
- adaptive support ventilation
 - in active condition, 191
 - description of, 187–188
 - in passive condition, 190
 - in pediatrics, 191
 - principles of, 188, 189
 - settings, adjustments and monitoring, 188, 190
 - in weaning phase, 191
 - NAVA (*see* Neurally adjusted ventilatory assist (NAVA))
 - passive measurement of respiratory resistance, 434–435
 - pressure-support ventilation
 - asynchrony, 175–179
 - breathing patterns, 173–174
 - definition of, 172–173
 - disadvantage of, 174
 - gas exchange, 173
 - noninvasive ventilation, 174
 - oxygenation, 173
 - phases of, 173
 - vs. SIMV, 174
 - uses of, 174
 - volume support ventilation, 175
 - work of breathing, 173
 - proportional assist ventilation
 - backup conventional ventilation, for apnoea/hypoventilation, 182
 - breathing control, 186
 - chest wall distortion, 185–186
 - clinical application, in infants, 180–182
 - elastance effect, 184–185
 - endotracheal tube leaks, 186
 - lung elastic recoil, compensation of, 186
 - pulmonary resistance, compensation of, 186
 - resistance effect, 185
 - in small animal species and infants, 186–187
 - strategy of, 180
 - technology, 182–184
 - terminology, 184
 - therapeutic objectives, 184
- Asthma, 90, 905–906
- assessment, 1315–1316
 - complications and management
 - endotracheal intubation, 1321
 - mechanical ventilation, 1321–1322
 - dynamic hyperinflation in, 1314
 - forced expiratory volumes, 90–92
 - inhalational gas uses
 - heliox, 1318
 - inhalational anesthetics, 1319
 - invasive mechanical ventilation, 1317–1318
 - lung V measurements, 91–93
 - noninvasive respiratory support, 1316–1317
 - pharmacologic treatment
 - anticholinergics, 1320
 - β_2 -adrenergic receptor agonists, 1319–1320
 - corticosteroids, 1320
 - magnesium, 1320
 - methylxanthines, 1320–1321
 - pulmonary mechanics changes, 1314–1315
 - R measurement, 91–92
 - strategies
 - for intubation, 1317
 - for mechanical ventilation, 1317
- Atelectasis
- absorption, 129
 - HFOV, 563
- Atelectatic lung disease, 1175–1177
- Atelectotrauma, 562
- Atelectrauma, VALI
- in neonatal intensive care unit, 920
 - in pediatric intensive care unit, 928–929
- Atracurium, 1025, 1050
- Atropine, use of, 1372
- Auto-cycling, 167
- Automatic FiO₂ adjustment, in neonates, 1447
- effects on
 - oxygenation and oxygen exposure, 1448–1450
 - staff workload, 1450
 - efficacy and beneficial effects, 1448
 - indwelling PaO₂ electrodes, 1448
 - limitations, 1450–1451
 - SpO₂ measurements, 1447–1451
 - transcutaneous PO₂ electrodes, 1448
- B**
- Babylog 8000+ HFOV, 228–229
- Baby lung concept, 934, 936
- β_2 -adrenergic receptor agonists, for asthma treatment, 1319–1320
- Barotrauma, 1322
- HFOV, 560–561
 - VALI
 - in neonatal intensive care unit, 920
 - in pediatric intensive care unit, 927–928
- Bayley Mental and motor scales tests, 1495
- BCPS. *See* Bidirectional cavopulmonary shunt (BCPS)

- Bench testing, mechanical ventilators
 - accuracy, 1553
 - breathing program, 1554
 - breathing simulators, 1551
 - neonatal testing, 1554, 1555
 - pneumotachometer, 1552
 - tidal volumes exhalation, 1554
- Benzodiazepines, 1023, 1041–1042
- Beraprost, 824
- Bidirectional cavopulmonary shunt (BCPS), 1352–1353
- Bi-level positive pressure airway ventilation (BIPAP), 1298
- Bi-level PPV mode, for NMD patients, 1392
- Bioimpedance, EIT, 457–458
- Biotrauma
 - VALI, 921
 - coagulation factors, 930
 - hormones, 930–931
 - inflammatory cytokines, 929–930
 - lipid-derived mediators, 931
 - oxidants, 931
 - ventilator-induced lung injury, 562
- Blood gas
 - continuous intravascular, 382–383
 - intermittent, 380–382
 - monitoring
 - analysis of, 492
 - end-tidal monitoring, 493–494
 - saturation monitoring, 492–493
 - tissue monitoring, 493
 - transcutaneous monitoring, 493
- Blood-gas equilibrium, 47–48
- Bolus surfactant therapy, 1221
- Bosentan, 129, 827
- BPD. *See* Bronchopulmonary dysplasia (BPD)
- Bradycardia, 117, 118
- Breathing systems
 - carbon dioxide absorbers, 1508–1510
 - circle anesthesia, 1507–1508
 - gas source, 1503
 - Mapleson (*see* Mapleson breathing systems)
- Bronchial hyperresponsiveness, 84
- Bronchiolitis
 - ARDS and RSV, 1304–1305
 - assessment/supportive therapy, 1292
 - cytomegalovirus, 1291–1292
 - endogenous surfactant activity, 1308
 - extracorporeal membrane oxygenation, 1306–1307
 - and general supportive measures, 1291–1292
 - helium-oxygen gas mixtures, 1307–1308
 - HFOV, 1293, 1306
 - inhaled nitric oxide, 1308
 - lung-directed therapy, 1307
 - lung function and mechanics in, 1295–1296
 - mechanical ventilation, 1298
 - airway obstruction, 1302–1303
 - initial settings, 1298–1301
 - PEEP, 1301–1302
 - weaning from, 1303–1304
 - permissive hypercapnia, 1305–1306
 - respiratory failure
 - blood gases and, 1293–1294
 - mechanical ventilation, 1292–1293
 - respiratory support, 1296–1297
 - BIPAP, 1298
 - heated humidified HFNC, 1297–1298
 - nasal CPAP, 1298
 - noninvasive, 1297
 - respiratory syncytial virus, 1291
 - surfactant therapy, 1308
 - typical features, 1291–1292
- Bronchiolitis obliterans (BO), 95
- Bronchoalveolar stem cells (BASCs), 8
- Bronchodilators
 - for BPD, 1272
 - therapy, 848–849
- Bronchopulmonary dysplasia (BPD), 12, 82–84, 94, 136, 813
 - anti-inflammatory drugs, 1273
 - clinical presentation, 1267–1268
 - corticosteroids, 1273
 - definition, 1268–1271
 - fluid management and diuretics, 1272
 - HFJV, 581, 1179–1180
 - incidence, 1269
 - during infancy and early childhood, 94
 - inflammation, 1273
 - invasive conventional mechanical ventilation, 540, 541
 - management
 - bronchodilators, 1272
 - chronic diuretic therapy, 1272
 - fluid management and diuretics, 1272
 - mechanical ventilation, 1274–1275, 1476
 - noninvasive respiratory support, 519
 - nutrition, 1273–1274
 - oxygen therapy, 1274
 - physiologic definition, 1271–1272
 - prediction of outcome, 1271
 - prevention and treatment
 - beta-agonists, 899
 - diuretics, 899
 - erythromycin, 899
 - vitamin A, 898
 - vitamin E and antioxidants, 899
 - prolonged steroid therapy, 1273
 - pulmonary hypertension, 1273
 - pulmonary vasodilators, 1273
 - RDS, 1207
 - school-age children, 94–95
 - survivors of, 94
 - ventilator-associated lung injury, 922–923
- Bronchoscopy
 - diagnostic indications
 - hemoptysis and pulmonary hemorrhage, 1007–1008
 - lower airway assessment, 1005–1006
 - patency and position of endotracheal tubes, 1004
 - pneumonia, 1006–1007
 - tracheostomy evaluation, 1004
 - upper airway assessment, 1004–1005

- Bronchoscopy (*cont.*)
 equipment, 1003
 physiological effects and complications, 1001–1003
 safety and monitoring, 1003
 sedation and analgesia, 1003–1004
 therapeutic indications
 endobronchial toilet, 1008
 foreign body removal, 1010
 hemoptysis and pulmonary hemorrhage, 1011
 percutaneous dilatational tracheostomy, 1010
 selective intubation, 1008–1009
 tracheobronchial stent placement, 1010–1011
 whole lung lavage, 1009
- Bronchotron, 236–237
- Bubble-continuous positive airway pressure, 609
- Bunnell Life Pulse HFJV, 231, 233–234. *See also*
 High-frequency jet ventilation (HFJV)
- Butyrophenones, 1044–1045
- C**
- Caffeine
 effects and side effects, 1241, 1242
 VALI, 927
- Calliope α HFOV, 227
- Capnography
 alveolar plateau, 393
 end-tidal monitoring, 493
 exhaled CO₂ decrease, 393
 expiratory CO₂ increase, 393
 inspiratory baseline, 392–393
 phases, 389, 390
 time-based, 388–400
 of ventilated newborn, 392
 of ventilated surfactant-depleted tracheotomized piglet, 391
 volume-based (volumetric), 400–404
- Carbon dioxide
 absorbers
 baralyme, 1509
 carbon monoxide, 1510
 exhaled gases, 1508
 soda lime, 1509
 invasive conventional mechanical ventilation, 539
- Cardiopulmonary interactions, of right ventricle, 1154–1155
- Cardiopulmonary interactions, physiological changes
 PEEP, 1343
 positive intrathoracic pressure
 ARDS, 1343–1347
 and BCPS, 1352–1353
 on left heart function, 1340–1343
 on pulmonary blood flow, 1339–1340
 spontaneous ventilation, 1334–1336
 and systemic venous return, 1336–1339
 in tetralogy of Fallot/Fontan physiology, 1347–1352
 positive pressure ventilation
 and heart failure, 1356–1359
 in intracardiac shunts, 1355–1356
 and ventricle lesions, 1353–1355
- Cardiovascular dysfunction, invasive conventional MV
 pulmonary vascular resistance vs. lung volume, 550
 RV and LV load, 550, 551
 venous return vs. intrathoracic pressure, 549, 550
- Cardiovascular function
 optimization of, 1374–1375
 PEEP on, 1343
- Central chemoreceptors, 125–126
- Central hypoventilation syndrome (CCHS),
 NRS, 521
- Cerebral palsy, 1483
- CHD. *See* Congenital heart disease (CHD)
- Chemoreceptors
 central, 125–126
 peripheral, 126
- Chest drains, 955
- Chest physiotherapy (CPT)
 clinical recommendations for, 702–704
 effects of, 688–689
 indications for, 689–691
 modalities
 manual hyperinflation techniques, 693–694
 mobilisation techniques, 691–693
 percussion and vibration, 693
 postural drainage positions, 691, 692
- Chest wall compliance, 31, 217
 passive respiratory mechanics, 306
 in sepsis, 1376–1378
- Chest wall distortion, 32–33
- Chirajet ventilator, 234
- Chloral hydrate, 1043
- Chlorpromazine, 1044
- Chronic diuretic therapy, for BPD, 1272
- Chronic ILD, 85–87
- Chronic lung disease (CLD), 894, 906, 1223
 of infancy, 94 (*see also* Bronchopulmonary dysplasia (BPD))
- Chronic obstructive pulmonary disease (COPD), 1485
- Chronic respiratory failure
 bronchopulmonary dysplasia
 anti-inflammatory drugs, 1273
 bronchodilators, 1272
 chronic diuretic therapy, 1272
 clinical presentation, 1267–1268
 corticosteroids, 1273
 definition, 1268–1271
 fluid management and diuretics, 1272
 incidence, 1269
 inflammation, 1273
 management, 1272
 mechanical ventilation, 1274–1275
 nutrition, 1273–1274
 oxygen therapy, 1274
 physiologic definition, 1271–1272
 prediction of outcome, 1271
 prolonged steroid therapy, 1273
 pulmonary hypertension, 1273
 pulmonary vasodilators, 1273
 respiratory care in the infant with, 1274
 for NPPV, 525

- Circle anesthesia breathing systems
 - APR valve, 1508
 - standard anesthesia, 1507, 1508
- Cisatracurium, 1025, 1050–1051
- CLD. *See* Chronic lung disease (CLD)
- Clinical Decision Support Systems (Clinical DSS), 1436
- Clinical pulmonary infection score (CPIS), 967–969
- Clonidine, 1038–1039, 1045
- Closed-system suctioning (CSS), 697, 698
- CMV. *See* Controlled mechanical ventilation (CMV)
- Codeine phosphate, 1037
- Collapsible upper airway segment concept, 316–318
- Computed tomography (CT)
 - lung volume measurements, 320–321
 - lung volume monitoring
 - acute respiratory distress syndrome, 451, 452
 - atelectasis, 452, 453
 - limitations of, 454
 - lung densities, 451, 452
 - measurements of, 453–455
 - superimposed pressure effects, 451, 452
 - prone position, ALI, 673, 674
- Congenital diaphragmatic hernia (CDH), 16, 81–82
 - delivery room resuscitation and stabilisation, 1226
 - epidemiology, 1225
 - extracorporeal membrane oxygenation, 1230–1231
 - HFOV, 647
 - intensive care management, 1226
 - nitric oxide, 813
 - outcomes, 1231–1232
 - permissive hypercapnia, 735
 - pre- and postoperative ventilation, 1226–1227
 - pulmonary vascular management, 1228–1230
 - surfactant replacement therapy, 893–894
 - surgical repair and thoracic compliance, 1227–1228
- Congenital heart disease (CHD), 1154
 - nitric oxide, 813–814
 - permissive hypercapnia, 735–736
 - TC-CO₂ monitoring, 408
- Constant flow methods, 325
- Constant-flow ventilation, 153–154, 325
- Continuous-flow ventilation, 151–152
- Continuous positive airway pressure (CPAP), 397
 - airway pressure adjustments, 1074, 1077–1078
 - applications, 1079
 - bubble CPAP, 609
 - devices for, 610
 - failure criteria, 1077–1079
 - HFNC, 1297
 - high-flow CPAP, 610
 - home NPPV, 285
 - indications
 - Benveniste device, 1074
 - clinical studies, 1074
 - oesophageal and diaphragmatic pressure time product, 1075
 - respiratory distress management, 1073
 - initiation
 - acute bronchiolitis, 1075
 - clinical asthma score, 1075–1076
 - Infant Flow®, 1076
 - respiratory deterioration prevention, 1077
 - stable positive expiratory pressure, 1076
- MAS, 1219
- nasal, 1298
- nasally delivered ventilation modes, 1427
- noninvasive, use of, 1359–1360
- RDS, 1192–1195
- respiratory system, 206
- side effects, 1078–1079
- ventilator-associated lung injury, 922
- weaning from mechanical ventilation, 1427
- Continuous tracheal gas insufflation (CTGI)
 - on alveolar gases, 248, 249
 - animal studies, 250
 - assembly diagram for, 249
 - CO₂ removal, 245
 - during expiratory phase, 248–249
 - human studies, 250–251
 - in neonates
 - alveolar disease, 583–584
 - factors influencing, 584
 - during prolonged period, 584–585
 - in neonatology, 251
 - physiological consequences of, 248–250
 - safety considerations, 249–250
 - test lung model
 - endotracheal tube/catheter characteristics, 246, 247
 - flow rates, 246, 247
 - PCO₂ reduction, 246–248
- Controlled mechanical ventilation (CMV), 397
 - FRC, 1513
 - vs. HFOV and HFJV, 222
 - inspiratory times, 1512
 - passive measurement of respiratory resistance, 435
 - pressure limit, 1511
- Controlled ventilatory modes, 161
 - assist/control ventilation, 164–165
 - control variables, 162–163
 - intermittent mandatory ventilation, 164
 - patient-triggered ventilation
 - abdominal motion, 166
 - airway pressure and flow, 166
 - auto-cycling, 167
 - graphic representation of, 172
 - neural triggering, 167
 - performance of, 165–166
 - thoracic impedance, 166
 - trigger systems, 166
 - peak inspiratory pressure, 162
 - phase variables, 170
 - cycle variables, 163–164
 - limit variables, 163
 - trigger variables, 163
 - synchronized intermittent mandatory ventilation, 164
 - synchronized ventilation, principles of, 165
 - waveforms, 162

- Controller waveform analysis, 208
- Conventional mechanical ventilation, 149
- constant-flow ventilation, 153–154
 - continuous-flow ventilation, 151–152
 - vs. HFOV and HFJV, 222
 - negative-pressure ventilation, 150
 - positive-pressure ventilation, 150
 - respiratory system compliance
 - dynamic hyperexpansion identification, 428
 - optimising PEEP, 424–428
- RIP
- EELV assessment, 444–445
 - tidal volume and breathing patterns
 - assessment, 447
 - variable-flow ventilation, 152–153
 - ventilator-associated lung injury
 - baby lung concept, 936
 - limiting airway pressure, 935
 - low tidal volume, 935
 - oxygen, 935
 - positive end-expiratory pressure, 935–936
- COPD. *See* Chronic obstructive pulmonary disease (COPD)
- Corticosteroids
- for asthma treatment, 1320
 - for BPD, 1273
 - CLD, 897
 - meconium aspiration syndrome, 897
 - post-extubation stridor, 992–993
 - RDS, 896
 - therapy, 1222
 - weaning from mechanical ventilation, 1428–1429
- CPAP. *See* Continuous positive airway pressure (CPAP)
- Critical illness myopathy (CIM), 1493
- Critical illness polyneuropathy (CIP), 1493
- Croup, 906
- CTGI. *See* Continuous tracheal gas insufflation (CTGI)
- Cycling-off parameter, 212
- Cystic fibrosis (CF)
- FEVs and FEFs, 92
 - lung V measurements, 92–93
 - noninvasive respiratory support, 519
 - ventilatory defect, 93–94
- D**
- Dead space (physiology), 159–160
- and alveolar ventilation, 396–397
 - ventilation assessment, 404
- Denver developmental screening test, 1495
- Desflurane, physical properties, 864–866
- Dexmedetomidine, 1039
- Diaphragmatic hernia, HFOV, 569
- Diaphragmatic palsy (DP)
- clinical diagnosis/severity assessment, 1325–1326
 - management, 1326–1328
 - phrenic nerve injury, 1325
- Diazepam, 1041–1042
- Diuretics, 899, 926, 1205–1206, 1272
- DMD. *See* Duchenne muscular dystrophy (DMD)
- Down's syndrome, NRS, 522
- Doxapram, 1428
- DP. *See* Diaphragmatic palsy (DP)
- Dragonfly HFOV, 228
- Drug nebulization, mechanical ventilation
- aerosol drug delivery
 - advantages, 838
 - characteristic and behavior, aerosols, 839–841
 - humidification of inhaled gas, 846
 - infant vs. adult lung, 838
 - liposome encapsulation, 838
 - location of aerosol generator, 845–846
 - metered-dose inhalers, 843–845
 - pneumatic nebulizers, 841–843
 - types of aerosol generators, 841
 - ventilator settings, 847
 - vibrating mesh nebulizers, 843
 - aerosolized antibiotics
 - recommendations, 853
 - therapy, 851–852
 - ventilated patients, 853
 - ventilator-associated pneumonia prevention, 852–853
 - bronchodilator therapy, 848–849
 - inhaled corticosteroids
 - methods of delivery, 854–855
 - side effects, 856
 - therapeutic uses, 855–856
 - inhaled selective pulmonary vasodilators, 850–851
- Drug weaning
- neuromuscular blockade
 - neonatal ICU, 1026
 - pediatric ICU, 1052
 - pain control, neonatal ICU, 1022
 - sedation
 - neonatal ICU, 1024
 - pediatric ICU, 1048–1049
- Duchenne muscular dystrophy (DMD), 89–90, 97, 1389
- Dynamic bedside assessment, 436
- Dynamic hyperexpansion, 428
- Dynamic hyperinflation, 307
- airway graphics, 1154
 - intrinsic PEEP, 1153–1154
 - overdistension, 1152–1153
- Dynamic pressure-volume-loop analysis
- during conventional ventilation, 424–428
 - during HFV, 428–434
- Dysanapsis, 71
- E**
- ECM. *See* Extracellular matrix (ECM)
- ECMO. *See* Extracorporeal membrane oxygenation (ECMO)
- ECP. *See* Explicit computerized protocols (ECP)
- Elastance
- definition of, 307
 - passive respiratory system, 307
 - proportional assist ventilation, 184–185

- Electrical impedance tomography (EIT)
 - lung volume monitoring
 - advantages and disadvantages of, 465–466
 - clinical experience, 464–465
 - data acquisition, 458
 - electrical bioimpedance, 457–458
 - functional EIT scans, 462–464
 - image interpretation, 459–461
 - image reconstruction, 459
 - limitations, 465–466
 - measuring principle of, 458
 - perspectives, 466
 - qualitative analysis, 459–461
 - tidal volume distribution, 462, 463
 - tracking regional lung volumes, 461–463
 - respiratory monitoring, 496
- End-expiratory lung volume (EELV), 422, 423
- neonatal ICU
 - absorption atelectasis, 1114
 - benefits of positive end-expiratory pressure, 1112
 - inflation limb pressure-volume curve, 1112–1113
 - inflection point, 1112
 - open lung concept, 1113
 - oxygenation, 1110
 - stepwise vital capacity manoeuvre, 1111
 - tidal breath compliance, 1111
 - venoarterial shunting, 1112
 - ventilation changes, effect of, 1110
- in RIP, 443–444
 - conventional mechanical ventilation, 444–445
 - high-frequency ventilation, 445–446
 - non-invasive ventilation, 446–448
- Endoglin, 17
- Endothelin receptors antagonists, 129
 - ambrisentan and sitaxentan, 827–828
 - bosentan, 827
 - pathway, 826
 - vasointestinal peptide, 828
- Endotracheal intubations, 402–403
 - on heart rate, 115–116
 - indications for, 117
- Endotracheal (ET) suctioning
 - adverse clinical effects, 694–695
 - catheter size selection, 698–699
 - clinical recommendations for, 702–704
 - depth of catheter insertion, 700–701
 - duration of, 700
 - frequency of, 696–697
 - on lung mechanics, 696
 - open-vs. closed-system, 697, 698
 - precautions and contraindications, 695–696
 - preoxygenation, 697–698
 - recruitment manoeuvres, 701–702
 - saline uses, 701
 - sterility, 700
 - vacuum pressure, 699–700
- Endotracheal tubes (ETT) placement, 400
- End-tidal carbon dioxide (etCO₂) monitoring, 388–400, 493–494. *See also* Time-based capnography
- Enflurane, physical properties, 864–866
- Epoprostenol, 128, 823–824
- Equal pressure point (EPP) concept, 315, 316
- Equation of motion, for respiratory system, 294
- ERT. *See* Extubation readiness test (ERT)
- Erythromycin, 899
- Esophageal manometry, 987–989
- etCO₂ monitoring. *See* End-tidal carbon dioxide (etCO₂) monitoring
- Eupnea
 - glottic aperture size and flow/volume control, 61
 - laryngeal intrinsic muscles in, 62–64
- Europe
 - caregiver coverage and role, 1583–1584
 - educational issues, 1586
 - equipment and monitoring, 1585
 - European Society of Pediatric and Neonatal Intensive Care, 1586
 - European Union of Medical Specialists, 1587
- Exercise capacity
 - beraprost, 824
 - bosentan, 825
 - epoprostenol, 823
 - morbidity, 1479
 - oxygen consumption, 1480, 1481
 - sildenafil, 821
 - sitaxentan and ambrisentan, 825
 - tadalafil, 821
 - treprostinil, 825
- Exogenous pulmonary surfactant
 - administration, 766–767
 - catheter/side port/suction valve, 768
 - chest position, 768–769
 - dual-lumen endotracheal tube, 768
 - slow infusion vs. bolus administration, 768
 - animal-derived surfactants
 - bovine surfactant, 765
 - porcine surfactant, 766
 - vs. protein-containing synthetic surfactants, 777–778
 - vs. protein-free synthetic surfactants, 776–777
 - arterial-to-alveolar oxygen tension ratio, 783
 - composition and metabolism, 761–763
 - in pediatric patient
 - animal studies, 787–788
 - bovine-derived surfactant, 784
 - dipalmitoyl phosphatidylcholine, 784
 - human studies, ALI/ARDS, 790–794
 - inhibition of surfactant, 786–787
 - pharmaceutical surfactants, 788–790
 - surfactant dysfunction, ALI/ARDS, 785–786
 - physiology
 - effect of mechanical ventilation, 765
 - injured neonatal lung, 764–765
 - normal lung, 763–764
 - premature lung, 764
 - porcine vs. bovine surfactants, 778–779
 - protein-containing vs. protein-free synthetic surfactants, 778

- Exogenous pulmonary surfactant (*cont.*)
- repeat doses, 776
 - respiratory distress syndrome
 - early vs. late treatment, 774–775
 - preterm infant, 774
 - respiratory management, 772–773
 - single vs. multiple doses, 775–776
 - synthetic surfactants, 766–767
 - therapy
 - acute respiratory distress syndrome, 782
 - adverse effects, 779–780
 - long-term respiratory outcomes, 781
 - meconium aspiration syndrome, 781–782
 - neurodevelopmental outcomes, 781
 - physical growth, 781
 - prophylactic surfactant, 769–772
 - rescue surfactant, 769–772
- Expiratory trigger (ET), 256, 285, 286, 617, 1090
- Explicit computerized protocols (ECP)
- challenges, 1443
 - clinical DSS, 1436
 - components of
 - control unit, 1440
 - input data, 1438–1439
 - output data, 1440
 - schematic illustration of, 1439
 - description of, 1435, 1437
 - development of
 - clinical team, 1437
 - instructions, 1438
 - iterative refinement, of rules, 1438
 - representative data, 1438
 - simplicity, 1438
 - variables and rules, 1437–1438
 - impact on health care, 1436
 - Smartcare/PS®
 - breathing pattern, 1441
 - description of, 1440–1441
 - end-tidal partial pressure of CO₂, 1441
 - respiratory rate, 1441
 - tidal volume, 1441
- External PEEP, 1318
- Extracellular matrix (ECM), 13–14
- Extracorporeal life support organization (ELSO)
- neonatal diagnoses, 1529, 1530
 - pediatric diagnoses, 1530
- Extracorporeal membrane oxygenation (ECMO),
- 80, 1202, 1306–1307
 - after bronchodilation, 81
 - for AHRF
 - complications, 1528–1529
 - indications and contraindications, 1528
 - outcome, 1529–1531
 - cannulation, 1526
 - HFOV, 647–648
 - oxygenators, 1526
 - patient management, 1527
 - pulmonary support, 1532
 - pumps, 1526
 - weaning, 1527
- Extrapulmonary ventilatory reflexes, 36
- Extrathoracic obstruction, 214
- Extubation
- failure, 1421
 - premature, 1415
 - readiness to, 1419–1420
 - success, predictive indices, 1420–1421
- Extubation readiness test (ERT), 1417–1419
- F**
- Fabian HFO, 228
- FACTT protocol, fluid management
- clinical trials, 716–718
 - conservative and liberal group, 717, 718
 - retrospective analysis, 719
 - two-by-two factorial design, 716
- Fatigue-resistant muscle fibers, 29
- Fentanyl, 1021, 1036
- Fetal inflammatory response syndrome, 921
- Fibroblast growth factor (FGF), 4, 14–16
- Fletcher's method, 396
- Flow asynchrony, 484–486
- Flow cycling technique, 163–164
- Flow-time waveform, 213
- characteristics of, 209, 210
 - constant-flow mode, 215–219
- Flow waveforms, 152, 162, 168, 169
- Fluid management
- in pediatric patient
 - ALI and ARDS, 714, 715
 - clinical outcomes, 716, 717
 - diuretic therapy, 719–720
 - early clinical trials, 716
 - FACTT protocol, 716–719
 - pathophysiology, 715
 - in preterm neonate
 - assessment of, 712
 - colloid infusions, 712, 713
 - creatinine, 712
 - level of, 713
 - sodium supplementation, 712
 - transepidermal water loss, 711
- Forced oscillatory techniques (FOT), 69–70, 309
- Foreign body aspiration, 1010
- Fraction of inspired oxygen (FiO₂)
- automatic adjustment of (*see* Automatic FiO₂ adjustment, in neonates)
 - concentration, 1117–1118
- Functional residual capacity (FRC), 422, 423, 428
- controlled ventilation, 1513
 - low resting volume, 33
 - respiratory system, 206
- G**
- Gas exchange
- alveolar ventilation
 - alveolar gas equation, 44–45
 - and alveolar PO₂, 43–44

- blood-gas equilibrium, 47–48
- Bohr equation, 47
- dead space, 47
- Fick's law, 47–48, 50
- interpretation of blood gases, 51–52
- intrapulmonary shunt
 - fraction estimation, 46
 - hypoxemia, 46
 - V/Q matching, 45
- metabolic rate, 50–51
- pulmonary, 43
- rates, 47
- tissue oxygenation, 49–50
- Gasping, 1606
- Gastroesophageal reflux, 1274
- Glasgow Coma Scale (GCS) score, TBI, 545
- Glucocorticoids (GC), 15–16
- Graft *versus* host disease (GVHD), 95
- Gravitational theory, 672
- Gross air leaks
 - airway and alveolar rupture
 - consequences, 948
 - pathophysiology, 947–948
 - incidence and risk factors, 948–950
 - pneumomediastinum, 952, 955–956
 - pneumopericardium, 952–953, 956
 - pneumoperitoneum, 953, 956
 - pneumothorax, 950–951, 954–956
 - pulmonary interstitial emphysema, 950, 954
 - subcutaneous emphysema, 954
 - systemic air embolism, 953–954, 956
 - ventilated patients, 956–957
- Guanylate cyclase stimulators, 822
- Guillain–Barré syndrome, 549

- H**
- Haemodynamic instability, in sepsis, 1374
- Haloperidol, 1044–1045
- Halothane, physical properties, 864–866
- HBO. *See* Hyperbaric oxygen therapy (HBO)
- Heart failure
 - noninvasive CPAP in, 1359–1360
 - positive pressure ventilation and, 1356–1359
- Heart-Lung index (HLI), 1463
- Heart rate, endotracheal intubation, 115–116
- Heat and moisture exchangers (HMEs), 259, 278–279
- Heated humidifiers, 277–278
 - HFNC, 1297–1298
 - for NIV in children, 259
- Heinen + Löwenstein integrated HFO, 228
- Heliox, 905
 - asthma, 905–906
 - bronchiolitis, 906, 1307–1308
 - chronic lung disease, of prematurity, 906
 - croup, 906
 - intubated child, 1088
 - nebulisation source, 1088
 - noninvasive respiratory support, 526–528
 - noninvasive ventilation
 - and clinical experience, 1088–1089
 - in pediatric patients, 1089–1090
 - protocol, 1090–1093
 - post-extubation stridor, 991–992
 - properties, 1086–1087
 - RSV, 906
 - side effects, 1093
 - spontaneously breathing infant, 1087–1088
- Helium, in operating room, 1517–1518
- Helium-oxygen gas mixtures. *See* Heliox
- Hematopoietic stem cell transplantation (HSCT), 95
- Hemodynamic instability and shock, 525
- Hemoptysis and pulmonary hemorrhage, 1007–1008, 1011
- Hering–Breuer inflation reflex, 64, 65, 69, 70, 126
- HFFI. *See* High-frequency flow interrupters (HFFI)
- HFJV. *See* High-frequency jet ventilation (HFJV)
- HFNC. *See* High-flow nasal cannula (HFNC)
- HFOV. *See* High-frequency oscillatory ventilation (HFOV)
- HFV. *See* High-frequency ventilation (HFV)
- High-flow nasal cannula (HFNC), 145, 509
 - devices, 124
 - heated humidified, 1297–1298
- High-frequency flow interrupters (HFFI)
 - Bronchotron, 236–237
 - gas exchange principles, 236
 - Infant Star 950 ventilator, 235, 236
 - performance characteristics of, 237
 - VDR 4, 237
- High-frequency jet ventilation (HFJV), 1358–1359
 - abdominal distension, 580–581
 - air leak syndrome, 1177–1178
 - air leak syndromes, 578–579
 - atelectatic lung disease, 1175–1177
 - bronchopulmonary dysplasia, 1179–1180
 - Bunnell Life Pulse, 233–234
 - Chirajet ventilator, 234
 - continuous pulse oximetry, 1173
 - functioning and gas exchange principles, 231–232
 - hemodynamic status, 581
 - inadvertent PEEP, 1174
 - inspiratory time, 232
 - interhospital transport, 582
 - intraoperative use, 581–582
 - MAS, 1221
 - Monsoon jet ventilator, 234
 - nonuniform lung disease/PPHN, 579–580
 - in older infants and children, 582
 - Paravent PAT ventilator, 234
 - performance characteristics of, 234–235
 - positive end-expiratory pressure, 232
 - pulmonary hypoplasia, 581, 1180
 - RDS, 1202
 - first-line treatment, 577–578
 - rescue therapy, 577
 - restrictive disease, 1180
 - Sanders bronchoscope jet, 231
 - Servo Pressure, 1174
 - severe nonuniform lung disease/PPHN, 1178–1179

- High-frequency jet ventilation (HFJV) (*cont.*)
 spike formation, 231–232
 suctioning, 1174
 technical limitations, 235
 weaning, 1175
 Whisper Jet patient box, 235
- High-frequency oscillatory ventilation (HFOV),
 79, 80, 1284
 abdominal surgery/NEC, 647
 alveolar morphology, 224, 226
 animal studies, 645
 atelectotrauma, 562
 Babylog 8000+, 228–229
 barotrauma, 561
 biotrauma, 562
 bronchiolitis, 1293, 1306
 Calliope α HFOV, 227
 CDH, 647
 characteristics, 560
 classical indications, 565
 classification, 559
 clinical trials, 645–646
 CMV, 559, 560
 description of, 220
 developments, 230–231
 Dragonfly, 228
 ECMO, 647–648
 elective vs. rescue, 564
 Fabian HFO, 228
 gas-transport mechanisms and pressure damping,
 222, 223
 Heinen + Löwenstein integrated HFO, 228
 Humming V, 227
 indications, 569–570
 infants on, 649
 lung protective strategies, 562–565
 management
 extubation, 649
 flow, 648
 frequency and amplitude, 648
 inspiratory time, 648
 MAP, 648
 weaning, 648
 MAS, 1221
 Metran ventilators, 227
 neonatal intensive care unit
 first-line therapy, 568
 long-term outcome, 568
 short-term outcome, 565, 568
 in neonate
 air-leak syndromes, 1166–1167
 indication and general considerations,
 1161–1162
 infant respiratory distress syndrome, 1164–1165
 initial settings, 1162–1163
 lung hypoplasia, 1166
 meconium aspiration syndrome, 1165–1163
 respiratory monitoring, 1164
 ventilator settings, 1163–1164
 weaning, 1167
 non-piston and piston oscillators, 221–222
 operation and gas exchange, 560–561
 optimal frequency selection, 223
 oxygenation and optimal lung volume, 224–225
 pediatric HFOV
 gas exchange management, 1168–1170
 transition to conventional ventilation, 1170
 ventilator settings, 1168
 pediatric intensive care unit
 in acute respiratory distress syndrome, 570–572
 indications, 572–575
 performance characteristics of, 230
 physiology, 646
 piston HFO ventilators, 225
 PPHN and MAS, 647
 PRVC, 632
 R100, 227
 RDS, 647, 1201–1202
 in respiratory distress syndrome, 568–569
 SensorMedics 3100A, 225, 227
 SensorMedics 3100B, 227
 SLE 5000, 229–230
 Sophie ventilators, 227
 Stephanie ventilators, 227
 surgery, 647
 tidal volume, 222
 types, 561
 ventilator-associated lung injury, 924, 936
 VN500, 229
 volutrauma, 561
- High-frequency percussive ventilator (HFPV).
See Bronchotron
- High-frequency ventilation (HFV)
 respiratory system compliance
 alternatives to, 430–434
 carbon dioxide diffusion coefficient, 431–432
 difficulties in, 429
 mathematical assumptions, 429–430
 monitoring, 428–429
 transcutaneous measurement of CO₂, 432, 433
 wave form attenuation, 429
- RIP
 EELV assessment, 445–446
 tidal volume and breathing patterns assessment,
 446, 448
- High-speed interrupter technique (HIT), 82
 Hounsfield unit (HU) scale, 453, 454
 Humming V HFOV, 227
 Hygroscopic condenser humidifiers (HCH), 278–279
 Hyperbaric oxygen therapy (HBO), 125
 air emboli, 133
 CO poisoning, 133
 toxicity/complications, 133
 wound healing, 133
- Hypercapnia, 38
 HFOV, 563
 permissive (*see* Permissive hypercapnia)
 ventilator-associated lung injury, 924
- Hyperinflation techniques, 693–694
 Hypometabolism, 37

- Hypoplastic lungs, 647
- Hypothermia, 1093
- Hypoxaemia, 46, 1093
 - causes of, 45
 - fluids and nutrition, 608
 - handling, 607
 - positioning, 607–608
- Hypoxia, 37–38, 1282
 - bronchodilators, 1272
 - invasive conventional mechanical ventilation
 - causes and upper airway obstruction, 546
 - parenchymal lung disease, 546
 - V/Q mismatch, 547
- Hypoxic hypometabolism, 37
- I**
- Iloprost, 128–129, 824–825
- Immune response, anaesthetic agents, 1053–1054
- Imposed work of breathing, 160
- Indwelling PaO₂ electrodes, 1448
- Inertance, of respiratory system, 307
- Infant respiratory distress syndrome (IRDS), 1164–1165
- Infant Star 950 ventilator, 235, 236
- Infections
 - ventilator-associated pneumonia (*see* Ventilator-associated pneumonia (VAP))
 - ventilator-associated sinusitis, 975–976
- Inflammatory cytokines, VALI, 929–930
- Infrared (IR) spectrography, 389
- Inhalational anesthetics, 1319
- Inhaled corticosteroids (ICS)
 - methods of delivery, 854–855
 - side effects, 856
 - therapeutic uses, 855–856
- Inhaled nitric oxide (iNO)
 - delivery methods and interactions, 814–815
 - indications and outcome analysis
 - neonatal respiratory failure, 817–818
 - pediatric respiratory failure, 818
 - PPHN, 816–817
 - primary and secondary PHT, 818
 - MAS, 1222
 - in neonatal respiratory failure, 894–895
 - in pediatric respiratory failure, 904–905
 - side effects and safety issues, 815–816
- IntelliVent® ECP
 - activation of, 1460
 - characteristics of, 1456, 1457
 - in clinical practice, 1463–1464
 - CO₂ controller
 - goal of, 1460
 - patient active, 1460, 1461
 - patient passive, 1460, 1461
 - spontaneous breathing trial, 1461–1462
 - ventilatory support, decrease of, 1461
 - description of, 1455, 1460
 - O₂ controller
 - adjustments in, 1462
 - goal of, 1462
 - heart lung interaction index, 1463
 - PEEP thresholds, 1462–1463
 - spontaneous breathing trial, 1459
 - weaning steps, 1460
- Intercostal paralysis from poliomyelitis, 1599
- Intermittent blood gas sampling, 380–382
- Intermittent mandatory ventilation (IMV)
 - vs. assist/control ventilation, 172
 - description of, 164
- Intermittent positive pressure ventilation (IPPV).
See Assist control ventilation (ACV)
- Interrupter technique, 70, 310
- Intrapulmonary shunt gas exchange
 - fraction estimation, 46
 - hypoxemia, 46
 - V/Q matching, 45
- Intrathoracic pressure (ITP)
 - ARDS, 1343–1347
 - and bidirectional cavopulmonary shunt, 1352–1353
 - on left heart function, 1340–1343
 - on pulmonary blood flow, 1339–1340
 - spontaneous ventilation and normal heart, 1334–1336
 - and systemic venous return, 1336–1339
 - in tetralogy of Fallot/Fontan physiology, 1347–1352
- Invasive conventional mechanical ventilation
 - in neonatal patient
 - airway pressures, lung volume, 539–540
 - assessments of, 537–538
 - carbon dioxide, 539
 - contraindications of, 541
 - control of breathing system, 537
 - critical upper airway obstruction, 536
 - intrapulmonary conditions, 537
 - oxygen therapy, 538–539
 - pH, 539
 - respiratory pump failure, 536
 - short-and long-term outcomes, 540–541
 - in pediatric patient
 - airway integrity, 543–544
 - alveolar gas equation, 548
 - assessments of, 551–553
 - cardiovascular dysfunction, 549–551
 - cautions and contraindications, 553–554
 - hypercarbia, 547, 548
 - hypoxia, 546–548
 - lower airway obstruction, 547–548
 - neurologic dysfunction, 544–545
 - physiologic development, 542, 543
 - respiratory muscle insufficiency, 548–549
 - shock states, 549
 - short-and long-term outcomes, 554–555
 - sizes and developmental stage changes, 542
- Invasive mechanical ventilation, 154
 - mode of, 1129–1130
 - for oxygen delivery, 125
- Isoflurane, physical properties, 864–866
- Isothermic saturation boundary, 275
- ITP. *See* Intrathoracic pressure (ITP)

J

Juxta-capillary (J) receptors, 126

K

Ketamine, 1039

L

Laryngochemoreflex (LCR), 64–65

Laryngotracheomalacia, NRS, 519

Larynx functions, 60

eupnea, 61

integrative central control and effects, 61–62

intrinsic muscles

and control, 62

in eupnea and grunting, 62–64

laryngeal closure and protection, 61

Lavage therapy, 1222

LCR. *See* Laryngochemoreflex (LCR)

Least-squares regression method, 310–311, 430

Left ventricular dysfunction, 1138

Left ventricular interactions, 1155

Liquid ventilation, 252–254

bronchopulmonary dysplasia, 588

ECLS, 587–588

VLBW, 587

Lobar and segmental collapse, 1008

Lorazepam, 1041–1042

Lower airway assessment, 1005–1006

Lower respiratory tract disease, RSV, 1302, 1304, 1307

Low-frequency forced oscillation technique (LFOT),
70, 78

Lungs, 1467, 1471

ALI (*see* Acute lung injury (ALI))

asymmetric injury, 573

compliance, 31, 217, 306–307

computed tomography

acute respiratory distress syndrome, 451, 452

atelectasis, 452, 453

limitations of, 454

lung densities, 451, 452

measurements of, 453–455

superimposed pressure effects, 451, 452

computerized decision support tools

adult protocol tables, 1469–1470

aim of, 1468

ALI/ARDS, pediatric trials of, 1469

ARDSNet protocol, 1468

pediatric ventilation modes, 1468, 1469

electrical impedance tomography

advantages and disadvantages of, 465–466

clinical experience, 464–465

data acquisition, 458

electrical bioimpedance, 457–458

functional EIT scans, 462–464

image interpretation, 459–461

image reconstruction, 459

limitations, 465–466

measuring principle of, 458

perspectives, 466

qualitative analysis, 459–461

tidal volume distribution, 462, 463

tracking regional lung volumes, 461–463

hypoplasia, 1166

magnetic resonance imaging

hyperpolarised helium, 455

uses of, 454, 455

water content quantification, 455, 456

positron emission tomography, 455–456

protective strategies, 563–564

RIP (*see* Respiratory inductance plethysmography
(RIP))

tissue resistance, 296

Lung-ventilator unit, 293

M

Magnesium, for asthma treatment, 1320

Magnetic resonance imaging (MRI)

alveolar multiplication, 74

lung volume monitoring

hyperpolarised helium, 455

uses of, 454, 455

water content quantification, 455, 456

Mainstream capnometer, 159

Malignant hyperthermia, 871

Mandatory mechanical inflation, 161

Mapleson breathing systems

advantages, 1507

C circuit setup, 1505, 1506

circuits arrangement, 1504, 1505

D circuit, 1506–1507

E and F systems, 1507

Matrix metalloproteinases (MMPs), 13, 14

Mead–Whittenberger method, 308, 429–430,
435–436

Mechanical inflations. *See* Spontaneous respiration vs.
mechanical inflations

Mechanical ventilation, 403

COPD, 1485

exercise capacity

morbidity, 1479

oxygen consumption, 1480, 1481

guideline for end of life

DNR, 1607

family preparation, 1608

NMBAs, 1606

pharmacologic sedation, 1605

sedatives and analgesics, 1606–1607

treatments, 1605

intensive care, 610

long-term outcome, 1490–1491

lung function, 1484

lung growth and development, 1484

neonatal lung, 1475

neurodevelopmental outcomes, 1480

neurological and cognitive areas, 1483–1484

neurosensory problems and cognitive

functioning, 1483

- neuromuscular dysfunction, 1493
- observational studies
 - American Academy of Neurology, 1602
 - decision-making process, 1601
 - incidence, 1602
 - in neonatal intensive care unit, 1601
 - in pediatric intensive care unit, 1600
- parental perspectives on end-of-life care
 - child death, 1603
 - physician parent conference, 1604
- psychological/emotional morbidity
 - functional status score, 1494–1495
 - MODS, 1495–1496
 - PTSD, 1494
- quality of life after, 1496
- respiratory function, 1492–1493
 - long-term effects on, 1477–1479
 - short-term effects on, 1476–1477
- respiratory health, 1479
- short-term outcome, 1490–1491
- TC-CO₂ monitoring, 407–408
- upper airways, 1492–1493
- Mechanical ventilators
 - conventional (*see* Conventional mechanical ventilation)
 - designing
 - alarms, 1546–1547
 - APRV, 1546
 - battery capability, 1543
 - bench testing, 1551–1555
 - benefits, 1542
 - breath averaging vs. intra-breath feedback, 1545
 - clinical trial, 1555–1557
 - compressors, 1543
 - computer interface, 1543–1544
 - control variables, 1544–1545
 - cycling variables, 1545–1546
 - decision, 1557
 - evaluation, 1550–1551
 - financial analysis, 1549–1550
 - footprint/appearance, 1543
 - leak compensation, 1546
 - mobility, 1543
 - modes, 1544
 - quality, 1540
 - response time, 1546
 - technology assessment, 1541
 - tidal volume accuracy, 1547
 - tidal volume measurements, 1547–1548
 - tidal volume targeting, 1548–1549
 - triggering variables, 1545–1546
 - user interface, 1549
 - ventilator dyssynchrony, 1549
 - effectiveness, 1539
 - functional characteristics of
 - control variables, 207–211
 - cycle variables, 211–212
 - limit variable, 211
 - phase variables, 211
 - HFV (*see* High-frequency ventilation (HFV))
 - neonatal outcomes, 1537, 1538
 - requisites for, 150
 - visual representations, 1539
- Meconium aspiration syndrome (MAS)
 - adjunctive therapy, 892–893
 - bolus surfactant therapy, 1222
 - complications, 1223
 - continuous positive airway pressure, 1219
 - conventional mechanical ventilation, 1220–1221
 - corticosteroid therapy, 1222
 - epidemiology, 1218
 - exogenous surfactant therapy, 781–782
 - extracorporeal membrane oxygenation, 1222–1223
 - HFJV, 1221
 - HFOV, 647, 1221
 - incidence, 1218
 - inhaled nitric oxide, 1222
 - intubation, 1219
 - lavage therapy, 1222
 - lung mechanics and functional residual capacity, 1216–1217
 - lung–thorax compliance reduction, 80
 - oxygen therapy, 1218–1219
 - pathophysiology, 1214–1217
 - risk factors, 1218
 - short-and long-term outcomes, 1224
 - systemic steroids, 897
 - use of HFOV, 1165–1166
- Metered-dose inhalers (MDI), 843–845
- Methoxyflurane, 872–873
- Methylxanthines
 - for asthma treatment, 1320–1321
 - caffeine, 897–898
 - inhaled CO₂, 898
 - respiratory stimulants, 611
 - weaning from mechanical ventilation
 - corticosteroids, 1428–1429
 - doxapram, 1428
- Metran ventilators, 227
- Microvascular maturation, 16
- Midazolam, 900, 1041
- Milrinone, 128, 826, 896
- MLR method. *See* Multiple linear regression (MLR) method
- MMPs. *See* Matrix metalloproteinases (MMPs)
- Mobilisation techniques, chest physiotherapy, 691–693
- Monsoon jet ventilator, 234
- Morphine, 1021, 1035
- Motion-resistant pulse oximetry, 385, 386
- Mucopolysaccharidosis (MPS), 522
- Multiple linear regression (MLR) method
 - pressure–volume loop measurement, 334
 - respiratory resistance measurement, 436
- Multiple occlusion technique, 325
- Multiple organ dysfunction syndrome (MODS), 1495–1496

- Muscle contraction
 - into pulmonary ventilation, 29
 - translation of, 28–29
 - force generation, 29–30
 - lung and chest wall mechanics, 31
 - pressure generation, 30
- Muscles of respiration
 - accessory muscles, 127
 - expiratory muscles, 126
 - inspiratory muscles, 126
- Muscular dystrophy (MD), NRS, 521, 522
- N**
- Nasal continuous positive airway pressure (NCPAP), 56
 - categories of studies, 138
 - apnoea, 142–143
 - extubation, 142
 - infant, 143–144
 - model and animal, 144–145
 - respiratory distress, 140
 - resuscitation, 139–140
 - surfactant therapy in conjunction, 141–142
 - devices
 - bi-level, 138
 - bubble, 136
 - continuous-flow, 136–137
 - infant flow, 137
 - NIPPV, 138
 - variable-flow, 137–138
 - history, 135–136
 - nasal respiratory support, 1063–1064
 - NRS, 504–506, 508
 - in premature infant, 505–506
- Nasal flow
 - nasal respiratory support, 1065, 1066
 - for premature infants, 509
- Nasal intermittent mandatory ventilation (NIMV)
 - definition of, 507
 - endotracheal ventilation and bronchopulmonary dysplasia, 507
 - vs. NCPAP, 508
 - NSIMV, 507, 508
 - pressure support ventilation, 508
 - thoracoabdominal asynchrony, 509
 - uses, 506, 507
 - ventilator inflation, 1064
 - ventilator settings adjustment, 1065–1066
- Nasal intermittent positive pressure ventilation (NIPPV), 138
 - adjunctive therapies, 1427 (*see also* Adjunctive therapies)
 - complications, 1199
 - delivery, 1198
 - evolution of, 1198
 - indications for, use, 1198–1199
- Nasal synchronized intermittent mandatory ventilation (NSIMV), 507, 508, 1064
- NAVA. *See* Neurally adjusted ventilatory assist (NAVA)
- NCPAP. *See* Nasal continuous positive airway pressure (NCPAP)
- Negative-pressure ventilation (NPV), 150
 - in ARF, 592–593
 - and cardiac patients, 589–591
 - cardiovascular effects, 240–241
 - cardiac output, 241–242
 - left ventricular afterload, 242–243
 - pulmonary vascular resistance, 243
 - transmural pressure, 241–242
 - continuous negative extrathoracic ventilation, 239
 - control mode, 239
 - cuirass, 239
 - jacket ventilators, 238–239
 - and long-term use, 593
 - NEEP and bronchiolitis, 591
 - noninvasive ventilation, 591
 - respiratory distress syndrome, 591–592
 - respiratory effects, 239–241
 - tank ventilators, 238, 239
 - transpulmonary pressure, 239, 240
- Neonatal intubation
 - complications of, 117
 - hemodynamic changes
 - arterial blood pressure, 116
 - heart rate, 115–116
 - indications for, 117
 - neonatal upper airways, 117
 - neurological effects
 - intracranial pressure, 116–117
 - pain, 117
 - premedication use, 119
 - respiratory changes, 116
 - route of, 118–119
 - technical preparation, 118
 - tube positioning
 - intratracheal position, 119
 - tube length, 119
- Neonatal lung, 1475
- Neonatal patients
 - breathing pattern, 398–399
 - capnography technical limitations in, 399–400
 - lung growth, 398
 - respiratory time constant, 398
 - small airways, 398
- Neonatal pneumonia
 - epidemiology, 1210
 - incidence, 1210–1211
 - lung mechanics, 1209–1210
 - pathophysiology, 1209
 - respiratory support, 1211–1213
 - risk factors, 1211
 - short-and long-term outcomes, 1213
- Neonatal respiratory distress syndrome, 734–735
- Neonatal respiratory failure, 817–818
 - acute (*see* Acute neonatal respiratory failure)
 - adjunctive therapies
 - antenatal steroids, 887–889
 - corticosteroids, 896–897
 - methylxanthines, 897–898

- non-pharmacologic interventions, 900
- patent ductus arteriosus closure, drugs, 898
- prevention and treatment of BPD, drugs, 898–899
- pulmonary vasodilators, 894–896
- sedatives and analgesics, 899–900
- surfactant replacement therapy, 889–894
- pulmonary vasodilators
 - adenosine, 896
 - inhaled nitric oxide, 894–895
 - magnesium sulphate, 895–896
 - milrinone, 896
 - phosphodiesterase inhibitors, 895
- Neurally adjusted ventilatory assist (NAVA)
 - benefits of, 197
 - considerations for, 197
 - diaphragm unloading concept, 195
 - electrical activity of diaphragm, 192–194
 - NAVA level setting, 195, 196
 - patient-ventilator synchronization, 194
 - PEEP setting, 195–197
 - principle of, 194
- Neurologic dysfunction, 544–545
- Neuromechanical unit
 - chest wall distortion, 32–33
 - feedback regulation, 34–35
 - chemical feedback, 36–37
 - extrapulmonary ventilatory reflexes, 36
 - vagal feedback, 35–36
 - FRC buffers, 33
 - generalities, 27–28
 - low resting volume, 33–34
 - muscle contraction translation, 28–29
 - force generation, 29–30
 - lung/chest wall mechanics, 31
 - pressure generation, 30
 - neural output, 28–29
- Neuromuscular blockade
 - neonatal ICU
 - assessment, 1025–1026
 - drug weaning, 1026
 - indications, 1024–1025
 - pancuronium, 1025
 - succinylcholine, 1025
 - toxicity and side effects, 1026
 - pediatric ICU
 - atracurium, 1050
 - cisatracurium, 1050–1051
 - drug weaning, 1052
 - indications, 1049–1050
 - pancuronium, 1050
 - rocuronium, 1051
 - suxamethonium, 1051–1052
 - toxicity and side effects, 1053
 - train-of-four monitoring, 1052
 - vecuronium, 1050
- Neuromuscular disease (NMD)
 - F/V* curves, 97
 - lung *V*, 96–97
 - noninvasive respiratory support, 518, 521
 - NPPV in patients with, 1390–1392
 - limitations and side effects of, 1393–1394
 - PI_{max}/PE_{max} test, 97–98
 - respiratory muscles weakness, 1388–1390
 - respiratory *P*, 97–98
 - ventilate patients with, 1392–1393
- Neuromuscular scoliosis, 89–90
- NIPPV. *See* Nasal intermittent positive pressure ventilation (NIPPV)
- Nitric oxide (NO)
 - inhaled
 - delivery methods and interactions, 814–815
 - indications and outcome analysis, 816–818
 - MAS, 1222
 - in neonatal respiratory failure, 894–895
 - in pediatric respiratory failure, 904–905
 - RDS, 1205
 - side effects and safety issues, 815–816
 - pathway, 819–820
 - citrulline, 822
 - guanylate cyclase stimulators, 822
 - sildenafil, 821
 - tadalafil, 821
 - physiology
 - bronchopulmonary dysplasia, 813
 - congenital diaphragmatic hernia, 813
 - congenital heart disease, 813–814
 - developmental regulation, 810–811
 - normal respiratory system, 809–810
 - persistent pulmonary hypertension, 812–813
 - pulmonary vascular disease, 811–812
 - ventilator-associated lung injury, 925–926
- Nitroprusside, 128
- NIV. *See* Noninvasive ventilation (NIV)
- NMD. *See* Neuromuscular disease (NMD)
- Nonconventional ventilation modes
 - HFV
 - description of, 220
 - HFFI, 235–237
 - HFJV, 231–235
 - HFO, 220–231
 - types of, 220
 - liquid ventilation, 252–254
 - negative pressure ventilation, 238–243
 - TGI, 244–251
- Noninvasive positive pressure ventilation (NPPV), 992, 1316
 - aim of, 283
 - airway pressure settings and adjustments, 1083–1085
 - failure criteria, 1079, 1084
 - home ventilators
 - advantage of, 287
 - air leaks, 286
 - cough-assisted techniques, 287
 - CPAP, 285
 - in infants, 287–288
 - inspiratory and expiratory triggers, 285, 286
 - machine patient interfaces for, 286–287
 - nutritional support, 287
 - oxygen therapy, 287

- Noninvasive positive pressure ventilation (NPPV) (*cont.*)
- performance of, 284, 285
 - skin erythema/irritation, 286
 - sleep evaluations of, 287
 - systematic maxillofacial evaluation, 286–287
 - tidal volume, 284
- indications, 1078–1081
- initiation, 1081–1083
- limitations and side effects of, 1393–1394
- in NMD patients, 1390–1393
- NRS
- for acute respiratory failure patients, 524, 525
 - for chronic respiratory failure, 525
 - modes of, 524
 - noninvasive ventilation modality, 524
 - pressure-controlled methods, 523
 - volume-controlled methods, 523
- principles of, 283–284
- side effects, 1084, 1086
- Noninvasive respiratory support (NRS)
- in neonatal patient
 - adjunct therapies, 510–511
 - application, 1068–1069
 - contraindications for, 509–510
 - failure criteria, 1066
 - long-term side effects, 1067–1068
 - nasal continuous positive airway pressure, 504–506, 1063–1065
 - nasal flow, 509, 1065, 1066
 - nasal intermittent mandatory ventilation, 1064–1066
 - nasal prongs, 504, 1063–1064
 - NIMV (*see* Nasal intermittent mandatory ventilation (NIMV))
 - respiratory distress syndrome, 503, 504
 - resuscitation, 505
 - short-term side effects, 1066–1067
 - weaning, 1069
 - in pediatric patient
 - achondroplasia, 522, 523
 - adjuvant therapies, 526–528
 - alveolar hypoventilation, 520
 - ARF (*see* Acute respiratory failure (ARF), NIV)
 - Arnold–Chiari malformation, type II, 521
 - bronchopulmonary dysplasia, 519
 - central hypoventilation syndrome, 521
 - contraindications for, 525–526
 - CPAP, 523 (*see also* Continuous positive airway pressure (CPAP))
 - cystic fibrosis, 519
 - Down’s syndrome, 522
 - helium-oxygen mixtures (*see* Heliox)
 - laryngotracheomalacia, 519
 - mucopolysaccharidosis, 522
 - muscular dystrophy, 521, 522
 - neuromuscular disease, 521
 - noninvasive ventilation, 512–513
 - NPPV, 523–525 (*see also* Noninvasive positive pressure ventilation (NPPV))
 - Prader–Willi syndrome, 522
 - spinal muscular atrophy, 521
 - upper airway obstruction, 519
- Noninvasive ventilation (NIV), 408–409. *See also* Noninvasive respiratory support (NRS)
- acute respiratory failure
 - acute airway obstruction, 514, 515
 - acute pulmonary edema, 517, 518
 - algorithm for, 513, 517
 - autologous bone marrow transplant, 518, 519
 - bronchiolitis, 515
 - criteria for, 513
 - facilitate extubation and prevent reintubation, 518
 - indication for, 516–518
 - objectives of, 513, 516
 - palliative indication of, 519
 - pediatric indications of, 513, 514
 - in chronic pediatric pathologies, 519, 520
 - description of, 154
 - interface choice, 254–255
 - machine-patient interfaces
 - characteristics of, 256, 257
 - classes of, 256
 - helmets, 258–260
 - humidification, 259–260
 - limitations and adverse effects, 260–261
 - mouthpiece, 259
 - nasal mask, 256–257
 - oronasal mask, 257, 258
 - for oxygen delivery, 125
 - in pediatric patient, 512–513
 - PSV, 173, 637–68
- RIP
- EELV assessment, 446–448
 - tidal volume and breathing patterns assessment, 448–449
 - technical considerations, 255–256
- Nonnutritive swallowing (NNS), 60
- Non-opioid analgesics
- α -2 adrenoceptor agonists, 1038–1039
 - doses and clinically relevant side effects, 1037–1038
 - ketamine, 1039, 1049
 - local analgesia techniques, 1040
 - NSAIDs, 1039
 - paracetamol, 1039–1040
- Nonsteroidal anti-inflammatory drugs (NSAIDs), 1021, 1039
- Nonsteroidal anti-inflammatory therapy, 925
- Nonuniform lung disease, 1178–1179
- North Africa
- challenges, 1568–1569
 - educational issues, 1569
 - formal ICUs
 - caregiver coverage and role, 1567
 - equipment, 1567–1568
 - pediatric intensive care development, 1566
 - region’s profile and child health, 1565–1566
- North America
- caregiver coverage and role, 1571–1572
 - educational issues, 1572
 - equipment, 1572, 1573
- NPPV. *See* Noninvasive positive pressure ventilation (NPPV)

O

Obstructive sleep apnea (OSA), 58

Occlusion technique, 325, 434

One-lung ventilation (OLV), 1515–1517

Open ET suctioning (OES), 697, 698

Operating room

adjunctive agents

carbon dioxide, 1518–1519

helium, 1517–1518

nitric oxide and nitrogen, 1518–1519

OLV, 1515–1517

breathing systems

carbon dioxide absorbers, 1508–1510

circle anesthesia, 1507–1508

gas source, 1503

Mapleson, 1504–1507

intraoperative mechanical ventilation

controlled, 1511–1513

ICU setting, 1510

ICU ventilator, 1514–1515

spontaneous, 1513–1514

Opioids, 899–900

acute tolerance, 1035

alfentanil, 1036

choices and dose ranges, 1033–1034

codeine phosphate, 1037

fentanyl, 1036

morphine, 1035

pharmacokinetics, 1033

remifentanyl, 1036–1037

sedation, neonatal ICU, 1023

tramadol, 1037

Optodes, 382

Oxygenation

monitoring techniques

altitude effects, 379–380

blood gas measurements, 380–383

measures and derivatives of, 379

pulse oximetry, 383–387

technology creep, 375–376

of ventilated infants and children, 375–379

in sepsis, 1373–1374

Oxygen breathing, physiological effects

absorption atelectasis, 129

gas-dilution principle, 131

HBO, 132–133

hemodynamic effects, 130–131

pulmonary oxygen toxicity, 129

pulmonary vasodilatation, 127–130

respiratory control

central control, 126

effectors, 126–127

sensors, 125–126

ROP, 131–132

Oxygen cascade, 377

Oxygen delivery systems

high-flow devices

high-flow nasal cannula, 124

hyperbaric oxygen therapy, 125

invasive mechanical ventilation, 125

noninvasive ventilation, 125

non-rebreather face masks, 124–125

oxyhood, 125

partial rebreather face masks, 125

low-flow devices

nasal cannulae, 124

simple/venturi face mask, 124

tracheostomy collar, 124

Oxygen therapy

altitudes, 603, 604

for BPD, 1274

causes, 606

deterioration, 606

devices, 609

hypoxemia

clinical indications, 605

fluids and nutrition, 608

haemoglobin–oxygen dissociation curve, 604, 605

handling, 607

positioning, 607–608

threshold, 604

invasive conventional mechanical ventilation,

538–539

monitoring, 606–607

sources, 608–609

trials off, 607

ventilator-associated lung injury, 920–922, 924–925

Oxygen toxicity, 929

Oxyhemoglobin dissociation curve, 377, 378

P

Pain control

neonatal ICU, 1019–1020

assessment, 1021–1022

drug weaning, 1022

fentanyl, 1021

indications, 1020

morphine, 1021

nonsteroidal anti-inflammatory drugs, 1021

toxicity and side effects, 1022–1023

pediatric ICU

indications, 1032–1033

non-opioid analgesics (*see* Non-opioid analgesics)

opioids (*see* Opioids)

Pancuronium, 1025, 1050

Paracetamol, 1039–1040

Paralytic agents, 900, 1372

Paravent PAT ventilator, 234

Partial liquid ventilation (PLV), 1202

Passive flow-volume technique, 309–310

Passive respiratory system

airway resistance

inspiratory and expiratory resistance, 313

limitations, 313

pressure-time waveform, 313, 314

rapid airway occlusion, 312

chest wall compliance, 306

dynamic compliance, 312

dynamic hyperinflation, 307

elastance, 307

equation of motion, for SCM, 308

- Passive respiratory system (*cont.*)
- forced oscillation technique, 309
 - inertance, 307
 - interrupter technique, 310
 - least-squares regression method, 310–311
 - lung compliance, 306–307
 - Mead–Whittenberger technique, 308
 - measurement of, 308
 - Mortola–Saetta method, 309
 - occlusion technique, 305
 - passive flow-volume technique, 309–310
 - pressure-volume curves, 312, 313
 - resistance, 305–306
 - static compliance, 311
 - tissue damping, 307
 - volume corrected resistance, 309
- Patent ductus arteriosus (PDA), 8, 80, 898
- Patient-triggered ventilation, 1425–1426
- abdominal motion, 166
 - airway pressure and flow, 166
 - auto-cycling, 167
 - graphic representation of, 172
 - neural triggering, 167
 - performance of, 165–166
 - thoracic impedance, 166
 - trigger systems, 166
- Patient-ventilator asynchrony
- expiratory asynchrony, 486
 - factors, 481
 - flow asynchrony, 483–486
 - short and prolonged cycled asynchrony, 487, 488
 - termination asynchrony, 486
 - trigger asynchrony (*see* Trigger asynchrony)
- Patient-ventilator dyssynchrony, 392
- Patient-ventilator interactions
- airway loops, 1143–1144
 - airway obstruction, 1151–1152
 - airway scalars, 1143–1144
 - alveolar ventilation
 - respiratory acidosis, 1146
 - respiratory alkalosis, 1146–1147
 - ventilatory requirements, 1145
 - compressible volume loss, 154
 - dead space, 159–160
 - dynamic hyperinflation
 - airway graphics, 1154
 - intrinsic PEEP, 1153–1154
 - overdistension, 1152–1153
 - endotracheal tubes, 158–159
 - flow dys-synchrony, 1148–1149
 - hemodynamically unstable patient
 - cardiopulmonary interactions, 1154–1155
 - congenital heart disease, 1154
 - left ventricular interactions, 1155
 - imposed work of breathing, 160
 - invasive ventilation, 154
 - noninvasive ventilation, 154
 - patient circuit effects, 154, 158
 - PEEP
 - acute lung injury, 1149–1151
 - ventilation-perfusion mismatch, 1151
 - pressure-support ventilation, 160, 161
 - trigger dys-synchrony, 1147–1148
- PAWPs. *See* Pulmonary artery wedge pressures (PAWPs)
- PCO₂ reduction test, 584
- PDE-3 inhibitors, 826
- Peak cough flow (PCF), 98
- Peak inspiratory pressure (PIP), 162, 213, 922
- Pediatric Acute Lung Injury and Sepsis Investigator's (PALISI) Network, 1417
- Pediatric ICU setting, potent inhalational anesthetic agents
- delivery techniques
 - air-oxygen blender and vaporizer, 877
 - anesthetic conserving device, 878–880
 - draw-over vaporizers, 877
 - isoflurane concentration, 879–880
 - Servo 900C ventilator, 877–878
 - Servo 900D anesthesia machine, 876
 - environmental pollution and scavenging, 880–881
 - monitoring, 881–882
 - procedural sedation, 872–873
 - sedation, mechanical ventilation, 873–874
 - status asthmaticus treatment, 874–875
 - status epilepticus treatment, 875–876
- Pediatric logistic organ dysfunction (PELOD), 1490–1491
- Pediatric respiratory failure, 818
- PEEP. *See* Positive end-expiratory pressure (PEEP)
- Percutaneous dilatational tracheostomy, 1010
- Perfluorochemical (PFC) liquids
- cardiovascular impact, 254
 - chemical properties, 252–253
 - gas solubility properties, 252–253
 - ideal fluid properties, 253
 - lung mechanics
 - alveolar-capillary interface, surface tension, 253
 - gas exchange, 253–254
 - liquid breathing, 253, 254
 - pulmonary structure/function, 253
- Peripheral chemoreceptors, 126
- Permissive hypercapnia, 1305–1306
- acute respiratory distress syndrome, 736
 - acute severe asthma, 736
 - cellular and molecular effects
 - acidosis vs. hypercapnia, 732
 - modulation of free radical biology, 733–734
 - neutrophil activity and cytokine level, 733
 - regulation of gene expression, 732–733
 - congenital diaphragmatic hernia, 735
 - congenital heart disease, 735–736
 - insights
 - cardiovascular, 731
 - neurologic, 731–732
 - pulmonary, 730–731
 - limitations and contraindications
 - buffering hypercapnic acidosis, 737–738
 - immature brain, 736–737
 - intracranial pressure regulation, 737
 - pulmonary vascular resistance, 737

- neonatal respiratory distress syndrome, 734–735
- neonates
 - advantages, 744
 - disadvantages, 745
 - neutral/negative data, 746–747
 - potential benefits and risks, 744
 - respiratory distress (*see* Respiratory distress, neonates)
 - supportive data, 745–746
- persistent pulmonary hypertension of newborn, 735
- physiologic effects
 - cardiovascular system, 729
 - central nervous system, 728–729
 - pulmonary system, 728
- Permissive hypercarbia, 1374
- Persistent pulmonary hypertension (PPHN), 812–813
 - acute neonatal lung disease, 80–81
 - drugs
 - adenosine, 896
 - magnesium sulphate, 895–896
 - milrinone, 896
 - HFJV, 579–580
 - HFOV, 570, 647
 - inhaled nitric oxide, 816–817
 - permissive hypercapnia, 735
- Pertussis, 1376
- Pharmaceutical surfactants, 788–790
- Phasic high intrathoracic pressure support ventilation (PHIPS) study, 1357–1358
- Phasitron, 236
- Phenothiazines, 1043–1044
- Phosphodiesterase-5 inhibitor, 129
- Phosphodiesterase inhibitors, 820–821
 - for BPD, 1273
 - citrulline, 822
 - guanylate cyclase stimulators, 822
 - pulmonary vasodilators, 895
 - sildenafil, 821
 - tadalafil, 821
- Phrenic nerve stimulation (PNS), 1326
- PIP. *See* Peak inspiratory pressure (PIP)
- PIP reduction test, 584
- Piston HFO ventilators, 225
- Platelet-activating factor (PAF), 931
- Pneumatic nebulizers, 841–843
- Pneumomediastinum, 952, 955–956
- Pneumopericardium, 952–953, 956
- Pneumoperitoneum, 953, 956
- Pneumotachometer, 1552
- Pneumothorax, 950–951, 954–956
- Polysomnography, 1391
- Positive end-expiratory pressure (PEEP), 1131–1132
 - acute lung injury, 1149–1151
 - ARDS, 1343–1347
 - benefits of, 1112
 - bronchiolitis, 1301–1302
 - on cardiovascular function, 1343
 - dynamic hyperinflation, 1153–1154
 - external, 1318
 - HFJV, 232, 1174
 - impacts in ARDS, 1343–1347
 - intrinsic, 1153–1154
 - NAVA, 195–197
 - optimisation, dynamic compliance measurements/graphic analysis, 424–428
 - patient-ventilator interactions, 1153–1154
 - respiratory mechanics, 325–326
 - respiratory system, 206, 214
 - thresholds, 1462–1463
 - trigger asynchrony, 483–485
 - ventilation-perfusion mismatch, 1151
 - ventilator-associated lung injury, 935–936
 - ventilator settings, 1131–1132
- Positive-pressure ventilation (PPV)
 - and heart failure, 1356–1359
 - in intracardiac shunts, 1355–1356
 - and ventricle lesions, 1353–1355
- Positron emission tomography (PET), 455–456
- Posterior cricoarytenoids (PCA), 62
- Post-extubation stridor
 - anatomical considerations, pediatric airway, 982–983
 - endoscopy, 989
 - endotracheal intubation, complications of, 993
 - esophageal manometry, 987–989
 - pulsus paradoxus, 986–987
 - respiratory inductance plethysmography, 988, 990, 991
 - risk factors
 - age, 983
 - air leak test, 984
 - cuff leak volume, 984
 - length of intubation, 983
 - neurologic dysfunction, 983–984
 - spirometry, 986–987
 - treatment and prevention
 - corticosteroids, 992–993
 - heliox, 991–992
 - noninvasive positive pressure ventilation, 992
 - racemic epinephrine, 990–991
 - reintubation, 992
 - upper airway obstruction, 985–986
- Post-traumatic stress disorder (PTSD), 1494
- Potent inhalational anesthetic agents
 - end-organ effects
 - airway, respiratory system, and control of ventilation, 868
 - carbon monoxide toxicity, 871–872
 - cardiovascular system and hemodynamic effects, 869
 - central nervous system, 867–868
 - hepatic and renal function, 869–871
 - malignant hyperthermia, 871
- pediatric ICU setting
 - delivery techniques, 876–880
 - environmental pollution and scavenging, 880–881
 - monitoring, 881–882
 - procedural sedation, 872–873
 - sedation, mechanical ventilation, 873–874
 - status asthmaticus treatment, 874–875
 - status epilepticus treatment, 875–876

- Potent inhalational anesthetic agents (*cont.*)
- principles
 - chemical structure, 864–865
 - minimum alveolar concentration, 866–867
 - uptake and distribution, 865–866
- PPV. *See* Positive-pressure ventilation (PPV)
- Prader-Willi syndrome, NRS, 522
- Premature extubation, 1415
- Pressure control ventilation, 202, 625
- Pressure reduction test, 584
- Pressure-regulated volume control mode (PRVC)
 - in neonatal patients, 630–633
 - in pediatric patients, 633–634
- Pressure-support ventilation (PSV), 160, 161
 - asynchrony, 175–179
 - breathing patterns, 173–174
 - clinical use
 - in neonates, 635–636
 - in pediatric patients, 636–637
 - cycling off, 635
 - definition of, 172–173
 - disadvantage of, 174
 - expected physiologic effects, 635
 - gas exchange, 173
 - initiation, 634–635
 - for NMD patients, 1392–1393
 - noninvasive ventilation, 174, 637–638
 - oxygenation, 173
 - phases of, 173
 - vs. SIMV, 174
 - uses of, 174
 - volume support ventilation, 175
 - weaning protocol, 1418
 - work of breathing, 173
- Pressure-time index (PTI), 347–348
- Prolonged cycled asynchrony, 487, 488
- Prolonged steroid therapy, for BPD, 1273
- Promethazine hydrochloride, 1044
- Prone position, acute lung injury
 - check list, 681, 683–684
 - complications of
 - corneal edema and ulcerations, 681
 - dislodgement of tubes, 680
 - edema, 680
 - intra-abdominal pressure, 681
 - skin breakdown and ulceration, 681
 - contraindications for, 679–680
 - effectiveness and outcomes
 - ARDS, 677
 - clinical trials, 678, 679
 - functional residual capacity, 677
 - meta-analysis, 679
 - OI and P/F ratio, 677–679
 - in pediatric patients, 675–677
 - indications for, 679–680
 - long-term outcomes, 682
 - physiologic effects
 - in diseased lungs, 673–675
 - in normal lungs, 672–673
 - principles, 671–672
- Prophylactic surfactant therapy
 - with animal-derived surfactant, 770
 - with protein-free synthetic surfactant, 770
 - vs. rescue surfactant therapy, 771–772
- Propofol, 1042–1043
- Proportional assist ventilation (PAV)
 - backup conventional ventilation, for apnoea/hypoventilation, 182
 - breathing control, 186
 - chest wall distortion, 185–186
 - clinical application, in infants, 180–182
 - elastance effect, 184–185
 - endotracheal tube leaks, 186
 - lung elastic recoil, compensation of, 186
 - pulmonary resistance, compensation of, 186
 - resistance effect, 185
 - in small animal species and infants, 186–187
 - strategy of, 180
 - technology, 182–184
 - terminology, 184
 - therapeutic objectives, 184
- Prostacyclin, 128–129
- Prostanoids
 - beraprost, 824
 - epoprostenol, 823–824
 - iloprost, 824–825
 - treprostinil, 825
- PRVC. *See* Pressure-regulated volume control mode (PRVC)
- PSV. *See* Pressure-support ventilation (PSV)
- Pulmonary artery wedge pressures (PAWPs), 620
- Pulmonary blood flow, 403–404, 1339–1340
 - intrathoracic pressure on, 1339–1340
- Pulmonary dysfunction, 569
- Pulmonary edema, 1272
- Pulmonary function tests (PFT), 85–86
- Pulmonary gas exchange, 43
- Pulmonary haemorrhage, 893, 1223
- Pulmonary hypertension, 1273
- Pulmonary hypoplasia, 581, 1180
- Pulmonary interstitial emphysema (PIE), 950, 954
- Pulmonary oxygen toxicity, 129
- Pulmonary stretch receptors, 126
- Pulmonary vascular disease, 811–812
- Pulmonary vascular resistance (PVR), 127–129, 428, 1273
- Pulmonary vascular system development
 - in alveolar, 16–18
 - extrapulmonary vessels, 8
 - intrapulmonary vessels, 8–10
 - microvascular maturation, 16
- Pulmonary vasoconstriction, 127
- Pulmonary vasodilatation, 127–130
- Pulmonary vasodilators, 1273
 - endothelin receptors antagonists
 - ambrisentan and sitaxentan, 827–828
 - bosentan, 827
 - pathway, 826
 - vasointestinal peptide, 828

inhaled selective, 850–851
 in neonatal respiratory failure
 adenosine, 896
 inhaled nitric oxide, 894–895
 magnesium sulphate, 895–896
 milrinone, 896
 phosphodiesterase inhibitors, 895
 nitric oxide (*see* Nitric oxide (NO))
 in pediatric respiratory failure
 aerosolised prostacyclin, 905
 inhaled nitric oxide, 904–905
 PDE-3 inhibitors, 826
 prostanoids
 beraprost, 824
 epoprostenol, 823–824
 iloprost, 824–825
 treprostinil, 825
 Pulse oximetry, 383–387
 Pulsus paradoxus, 986–987, 1346
 PVR. *See* Pulmonary vascular resistance (PVR)

Q

Qualitative diagnostic calibration (QDC) algorithm,
 RIP, 443, 444

R

Racemic epinephrine, 990–991
 Raised volume rapid thoracic compression (RVRTC),
 69, 83
 Rapid airway occlusion, 311, 312
 Rapid eye movement (REM) sleep, 58, 59, 1390
 Rapid thoracoabdominal compression (RTC)
 technique, 69
 RDS. *See* Respiratory distress syndrome (RDS)
 Recruitment manoeuvres (RM), 701–702
 Relative humidity, 276
 Remifentanyl, 1036–1037
 Rescue surfactant therapy
 animal-derived surfactant, 769–770
 vs. prophylactic surfactant therapy, 771–772
 protein-free synthetic surfactant, 770
 Resistance, of respiratory system, 305–306
 Respirator cycle control modes
 assist-control ventilation (*see* Assist control
 ventilation (ACV))
 hybrid techniques
 breath-to-breath modes, 626
 PRVC (*see* Pressure-regulated volume control
 mode (PRVC))
 VAPS, 634
 volume guarantee and volume-targeted modes,
 629–630
 PCV, 625
 PSV, 634–637
 SIMV, 621–625
 volume control ventilation, 626
 Respiratory acidosis, 1146
 Respiratory alkalosis, 1146–1147

Respiratory distress, neonates
 mechanical ventilation, 752–753
 without intubation
 air leak syndromes, 750
 antenatal steroids, 749
 BPD/death, 751
 Columbia approach, 748
 CPAP strategy, 748
 delivery room management, 751
 extubation criteria, 749
 PaCO₂ level, 752
 pneumothorax, 749
 Scandinavian approach, 750
 surfactant administration, 748
 Respiratory distress syndrome (RDS)
 adjunctive therapies, 1203–1206
 antenatal steroids, 78
 classical complications, 1206–1207
 continuous positive airway pressure
 complications, 1195
 delivery room, 1194
 generation, 1193
 nasal interface, 1193–1194
 optimal pressure, 1194–1195
 post-extubation, 1194
 delivery room management, 1191–1192
 early *vs.* late treatment, 774–775
 epidemiology, 1189–1190
 extracorporeal membrane oxygenation, 1202
 general management, 1192
 HFJV, 1202
 first-line treatment, 577–578
 rescue therapy, 577
 HFOV, 1201–1202
 humidified nasal cannula oxygen delivery,
 1196–1197
 incidence, 1190
 INSURE technique, 1195–1196
 lung mechanics, 1188–1189
 nasal intermittent positive pressure ventilation
 complications, 1199
 delivery, 1198
 evolution, 1198
 indications, 1198–1199
 modes, 1197
 NRS (*see* Noninvasive respiratory support (NRS))
 partial liquid ventilation, 1202
 pathophysiology
 clinical picture, 1187–1188
 histology, 1187
 lung development, 1186
 physiology, 1187
 transition, 1186
 preterm infant, 774
 prophylactic surfactant therapy, 770
 rescue surfactant therapy, 769–770
 risk factors, 1190–1191
 short-and long-term outcomes, 1207–1208
 supplemental oxygen, 1192
 surfactant deficiency, 77–78

- Respiratory distress syndrome (RDS) (*cont.*)
 treatment, 79–80
 ventilation, 1199–1201
 weaning, 1202–1203
- Respiratory function
 long-term effects on
 airflow obstruction, 1479
 BPD, 1477–1478
 pulmonary, 1492
 short-term effects on
 infections, 1477
 morbidity, 1476
- VILI and VAP, 1492
- Respiratory health, 1479
- Respiratory inductance plethysmography (RIP)
 airway pressure changes, 449, 450
 chest wall muscle activity, 988
 EELV assessment, 443–444
 conventional mechanical ventilation, 444–445
 high-frequency ventilation, 445–446
 non-invasive ventilation, 446–448
 limitations of, 449
 oscillatory waves, 988, 990
 phase angles, 988, 991
 static pressure-volume curve, 327
 theoretical considerations
 calibration, 443, 444
 equipment, 442–443
 lung volume measurement, 441, 442
 principles, 441
 tidal volume and breathing patterns assessment
 conventional mechanical ventilation, 447
 high-frequency ventilation, 446, 448
 non-invasive ventilation, 448–449
 tidal ventilation, 447, 448
- Respiratory mechanical unloading (RMU).
 See Proportional assist ventilation (PAV)
- Respiratory mechanics
 airway gas flow
 laminar flow, 300
 Reynolds number, 301–302
 turbulent flow, 300–301
 airway pressure, 302–304
 airways and lung development, 70–73
 chest wall musculature, 74–76
 dynamic pressure-volume loop, 333–334
 least-squares regression method, 334
 Mead–Whittenberger analysis, 334
 multiple linear regression technique, 334
 ventilator display, 334–337
 dynamic tests of, 69–70
 dysanapsis, 71
 flow-time curve, 318–319
 flow-volume loop, 319, 320
 intrapulmonary pressure equilibration
 collapsible segment concept, 316–318
 equal pressure point, 315, 316
 intrauterine exposure, 72
 lung volume measurements
 computed tomography, 320–321
 dilution technique, 321
 error sources, 321–322
 limitations and drawbacks, 321–322
 trapezoidal rule, 320
 passive respiratory system (*see* Passive respiratory system)
 passive tests of, 68–69
 periconceptional exposure, 72
 respiratory monitoring, 355
 flow-volume loops, 360–362
 gas exchange, 356
 pressure-volume loops, 361, 363–366
 work of breathing, 356
 respiratory musculature, 74–76
 sex differences in, 71–72
 static pressure-volume curve
 clinical implication of, 332–333
 constant flow methods, 325
 construction of, 327
 CPAP steps technique, 324–325
 CT imaging, 327
 description of, 323
 during HFOV, 325, 326
 inflation and deflation of, 328–331
 lung volume measurements, 326–327
 multiple occlusion technique, 325
 reproducibility of, 327–328
 respiratory inductance plethysmography, 327
 stepwise PEEP maneuver, 325–326
 super-syringe technique, 323–324, 326–327
 ventilator technique, 327
 time constants
 expiratory, 318
 of lung, 314
 resistance and compliance, 358–359
 of respiratory units, 315
 transducers
 analog-to-digital converter, 298
 definition of, 297
 dynamic properties of, 297–298
 frequency response of, 298
 input impedance, 298
 for pressure and flow measurement, 299–300
 static properties of, 297
 transesophageal pressure, 304–305
 WOB measurement (*see* Work of breathing (WOB))
- Respiratory mechanics, in neonatal pathologies
 acute neonatal lung disease
 congenital diaphragmatic hernia, 81–82
 meconium aspiration syndrome, 80
 PPHN, 80–81
 respiratory distress syndrome, 78–80
 transient tachypnea of the newborn, 77
 chronic neonatal lung disease
 bronchial hyperresponsiveness, 84–85
 bronchopulmonary dysplasia, 82–84
- Respiratory mechanics, in pediatric diseases
 hematopoietic stem cell transplantation, 95
 neuromuscular disease
 F/V curves, 97
 lung V, 96–97

- P_Imax/P_Emax test, 97–98
- respiratory *P*, 97–98
- obstructive airway disease, 95
- obstructive lung disease
 - asthma/wheezing disorders, 90–92
 - cystic fibrosis, 92–94
 - long-term sequelae of NLD/CLD, 94–95
- restrictive defect in chest wall
 - obesity, 88
 - scoliosis, 89–90
- restrictive lung disease, 85
- restrictive ventilatory defect
 - ALI/ARDS, 87–88
 - chronic ILD, 85–87
- Respiratory monitoring, 491–492
 - airway pressure measurement, 495
 - blood gases
 - analysis of, 492
 - end-tidal monitoring, 493–494
 - saturation monitoring, 492–493
 - tissue monitoring, 493
 - transcutaneous monitoring, 493
 - clinical signs and significance, 492
 - electrical impedance tomography, 496
 - flow and volume measurement, 495
 - oxygenation
 - altitude effects, 379–380
 - blood gas measurements, 380–383
 - pulse oximetry, 383–387
 - of ventilated infants and children, 375–379
 - pressure-volume curves, 496
 - transcutaneous carbon dioxide monitoring, 405–411
 - ventilation
 - capnography, 388
 - time-based capnography/end-tidal carbon dioxide measurements, 388–400
 - volume-based (volumetric) capnography, 400–404
- Respiratory monitoring equipment
 - North Africa, 1568
 - North America, 1572, 1573
 - South America, 1579
- Respiratory muscles
 - insufficiency
 - Duchenne muscular dystrophy, 548
 - neuromuscular diseases, 548, 549
 - noninvasive ventilation, 548
 - spinal muscular atrophy, 548
 - weakness of, 1388–1390
- Respiratory physiotherapy. *See* Chest physiotherapy (CPT)
- Respiratory rate, 1116–1117
- Respiratory support, developing countries
 - CPAP, 609–610
 - mechanical ventilation, 610–611
 - methylxanthines, 611
 - oxygen therapy (*see* Oxygen therapy)
- Respiratory support equipment
 - Europe, 1585
 - North Africa, 1567, 1578
- Respiratory syncytial virus (RSV)
 - bronchiolitis (*see* Bronchiolitis)
 - lower respiratory tract disease, 1302, 1304, 1307
 - sepsis and, 1376
- Respiratory system
 - clinical implications
 - measurement to guide ventilation strategies, 436–437
 - progression of disease monitoring, 437
 - response to treatment, 437
 - dynamic pressure-volume-loop analysis
 - for disease evolution assessment, 423
 - for ventilator setting selection, 424–434
 - equation of motion for, 205, 206
 - factors for measurement of, 434
 - inspiratory flow opposing forces, 422
 - in intubated and non-intubated patients, 434
 - laryngeal and pump muscle
 - activities, 64–66
 - breathing, 64
 - central and chemical control, 66–67
 - laryngeal functions (*see* Larynx functions)
 - measurement methods
 - active measurements, 435–436
 - passive measurement, 434
 - technique, 434–435
 - mechanical properties, 68
 - mechanics
 - alternatives to respiratory system compliance, 430–434
 - mathematical assumptions of, 429–430
 - nasal functions
 - air conditioning, 56
 - nasal patency and resistance, 56–58
 - nasal reflexes and protection, 56
 - vascularity, 56
 - oral cavity/pharyngeal functions, 58
 - nonnutritive swallowing, 60
 - obstructive apnoea, 58–59
 - pharyngeal patency, 58
 - sucking–swallowing–breathing, 59
 - volitional swallowing, 60
 - postnatal
 - alveolarization, 10–11
 - alveoli formation, 11–12
 - ECM, 13–14
 - growth factors, 14–15
 - pulmonary vascular system, 16–18
 - transcription factors, 15
 - vascular growth, 18–19
 - prenatal
 - air-blood interface, 7–8
 - airway epithelium, 6–7
 - airways, 3–4
 - branching morphogenesis, 4
 - extrapulmonary vessels, 8
 - intrapulmonary vessels, 8–10
 - pulmonary vascular system, 8
 - pressure-volume relationship, 421–423
 - upper airway, 55

- Restrictive diseases, 1180
- Retinoic acid, 15–16
- Retinopathy of prematurity (ROP)
 - pathophysiology, 131–132
 - risk factors, 132
 - screening, 132
 - treatment, 132
- R100 HFOV, 227
- Right ventricular dysfunction, 1138
- Rocuronium, 1051
- ROP. *See* Retinopathy of prematurity (ROP)
- RSV and bronchiolitis, 902–903, 906

- S**
- Sanders bronchoscope jet, 231
- “SATI-Q” project, 1576
- SBT. *See* Spontaneous breathing trials (SBTs)
- Scoliosis, 89–90
- Sedation
 - neonatal ICU
 - assessment, 1023–1024
 - benzodiazepines, 1023
 - drug weaning, 1024
 - indications, 1023
 - opioids, 1023
 - toxicity and side effects, 1024
 - pediatric ICU
 - benzodiazepines, 1041–1042
 - butyrophenones, 1044–1045
 - chloral hydrate, 1043
 - clonidine, 1045
 - drug weaning, 1048–1049
 - electrophysiological measures, 1047–1048
 - indications, 1040–1041
 - non-pharmacological measures, 1046
 - observational measures, 1046–1047
 - phenothiazines, 1043–1044
 - propofol, 1042–1043
 - skin resistivity, 1048
 - toxicity and side effects, 1049
 - volatile agents, 1045–1046
- Seizures, invasive conventional mechanical ventilation, 545
- Seldinger technique, 1408
- SensorMedics 3100A, 225, 227
- SensorMedics 3100B, 227
- Sepsis, 1369, 1370
 - and acute lung injury, 1376
 - airway humidification and clearance in, 1378
 - and ARDS, 1376
 - blood gas and values maintenance
 - carbon dioxide, 1374
 - oxygenation, 1373–1374
 - chest wall compliance in, 1376–1378
 - damage to lungs, 1375–1376
 - drugs for intubation
 - atropine, 1372
 - paralytic agents, 1372
 - infection control issues, 1378
 - initiation of ventilation, 1372
 - optimization of cardiovascular function, 1374–1375
 - and organ failure, 1377
 - and pertussis, 1376
 - and RSV infection, 1376
 - and tuberculosis, 1376
 - ventilatory support, 1371
- Septic shock, 1371
- Servo 900C ventilator, 877–878
- Sevoflurane, physical properties, 864–866
- Short cycled asynchrony, 487, 488
- Sidestream capnometer, 159
- Sildenafil, 129, 821
- SIMV. *See* Synchronized intermittent mandatory ventilation (SIMV)
- Single-breath carbon dioxide (SBCO₂) elimination. *See* Volumetric capnography
- Single-breath CO₂ (SBCO₂) technique, 396
- Single breath occlusion technique, 434
- Single-compartment model (SCM), equation of motion for, 308
- SIRS. *See* Systemic inflammatory response syndrome (SIRS)
- SLE 5000, 229–230
- Small airway disease, 572, 1137
- SmartCare/PS® ECP
 - breathing pattern, 1441
 - characteristics of, 1456, 1457
 - classification of ventilation, 1458
 - in clinical practice, 1459–1460
 - description of, 1440–1441, 1455, 1456
 - end-tidal partial pressure of CO₂, 1441
 - initiation of, 1456–1458
 - normal ventilation, 1458
 - phases of, 1456
 - randomised clinical trial, 1459
 - respiratory rate, 1441
 - spontaneous breathing trial, 1458–1459
 - tidal volume, 1441
 - weaning, of ventilatory support, 1458
- SMAs. *See* Spinal muscular atrophies (SMAs)
- Sniff nasal inspiratory pressure (SNIP), 98
- Sophie ventilators, 227
- South America
 - caregiver coverage and role, 1577–1578
 - educational issues, 1579
 - equipment
 - interfaces, 1578–1579
 - monitoring, 1579
 - respiratory support, 1578
 - ventilator modes and setting, 1579
 - outcome, 1579–1580
 - population characteristics
 - baseline, 1576
 - PICU, 1577
 - primary reason, 1577
- Spinal muscular atrophies (SMAs), 96, 521, 1389
- Spirometry, 986–987

- Spontaneous breathing trials (SBTs), 1416, 1420
 - IntelliVent[®] ECP, 1459
 - SmartCare/PS[®] ECP, 1458–1459
 - Spontaneous mechanical inflation, 161
 - Spontaneous respiration vs. mechanical inflations
 - muscle and reflex feedback system, 473, 474
 - Newton's equation of motion, 473
 - patient-related factors
 - P_{mus}* waveform characteristics, 479–481
 - respiratory system mechanics, 479–481
 - patient-ventilator asynchrony
 - expiratory asynchrony, 486
 - factors, 481
 - flow asynchrony, 483–486
 - short and prolonged cycled asynchrony, 487, 488
 - termination asynchrony, 486
 - trigger asynchrony (*see* Trigger asynchrony)
 - ventilator-related factors
 - cycle off variable, 478–479
 - pressure delivery, 476–478
 - pressure generation, 474, 475
 - trigger variable, 474–477
 - Spontaneous ventilation, 408–409, 1513–1514
 - Stacked breaths, trigger asynchrony, 482, 483
 - Static pressure-volume curve, respiratory mechanics
 - clinical implication of, 332–333
 - constant flow methods, 325
 - construction of, 327
 - CPAP steps technique, 324–325
 - CT imaging, 327
 - description of, 323
 - during HFOV, 325, 326
 - inflation and deflation of
 - anatomical and physiological correlates of, 329–331
 - features of, 328–329
 - modeling of, 331
 - lung volume measurements, 326–327
 - multiple occlusion technique, 325
 - reproducibility of, 327–328
 - respiratory inductance plethysmography, 327
 - stepwise PEEP maneuver, 325–326
 - super-syringe technique, 323–324, 326–327
 - ventilator technique, 327
 - Status asthmaticus, 874–875
 - Status epilepticus, 875–876
 - Stephanie ventilators, 227
 - Steroid therapy, 925
 - Subcutaneous emphysema, 954
 - Subglottic stenosis, for tracheostomy, 1402, 1405
 - Succinylcholine, 1025
 - Sudden infant death syndrome (SIDS), 30, 58
 - Sulfur-containing amino acids, deficiency, 1274
 - Superior laryngeal nerve (SLN), 64, 65
 - Super-syringe technique, 323–324, 326–327
 - Surfactant replacement therapy (SRT)
 - beractant vs. calfactant vs. poractant alpha, 890–891
 - chronic lung disease, 894
 - congenital diaphragmatic hernia, 893–894
 - in developing countries, 891–892
 - INSURE technique, 890
 - late preterm RDS, 893
 - meconium aspiration syndrome, 892–893
 - neonatal mortality reduction, 889
 - in newborns, 892
 - pneumonia, 893
 - pulmonary haemorrhage, 893
 - respiratory insufficiency, 889–890
 - Surfactants
 - noninvasive respiratory support, 510–511
 - in pediatric respiratory failure
 - acute respiratory failure, ALI and ARDS, 902–903
 - animal-derived, 902
 - hypoxemia, 901
 - iatrogenic lung haemorrhage, 903
 - Pneumocystis jirovecii* infection, 904
 - RSV and bronchiolitis, 902–903
 - Suxamethonium, 1051–1052
 - Synchronized intermittent mandatory ventilation (SIMV)
 - cycle time settings, 623
 - expected physiologic effects, 623
 - in neonatal patient, 624
 - in pediatric patient, 624–625
 - PEEP, 164
 - pressure and flow triggering, 622–623
 - for ventilator weaning, 625
 - Synchronized ventilation, principles of, 165
 - Synthetic surfactants
 - animal-derived
 - vs. protein-containing, 777–778
 - vs. protein-free, 776–777
 - protein-free
 - dipalmitoylphosphatidylcholine, 766
 - prophylaxis, 770
 - vs. protein-containing, 778
 - rescue therapy, 770
 - Systemic air embolism, 953–954, 956
 - Systemic inflammatory response syndrome (SIRS), 1370
 - Systemic steroids, 896–897
- T**
- Tadalafil, 821
 - T_cPO₂. *See* Transcutaneous PO₂ (T_cPO₂)
 - T_cPO₂ electrodes, 1448
 - Tenascin-C, 13
 - Tension-time index (*P_{TP}*), 348
 - of the diaphragm (TTdi), 1427
 - Tenting technique, chest physiotherapy, 693
 - Terbutaline, for asthma treatment, 1319
 - Thyroarytenoids (TA), 62
 - Tidal ventilation. *See* Conventional mechanical ventilation
 - Time-based capnography
 - alveolar ventilation and dead space, 396–397
 - and endotracheal tube placement, 400
 - interpreting capnograms, 392–393
 - methods, waveforms and nomenclature, 388–389
 - neonatal patient
 - capnography technical limitations in, 399–400
 - considerations in, 398–399

Time-based capnography (*cont.*)

NPPV, 397–398

 $P_{a-et}CO_2$ difference and ventilation/perfusion abnormalities, 395 $P_{et}CO_2$ monitoring, 389–392

capnogram, 390–392

clinical factors, 389, 390

and P_aCO_2 relationship, 394–395

prerequisite for, 389

Tissue damping, 307

Tissue inhibitor of metalloproteinases (TIMPs), 13

Tissue oxygenation, 49–50

Tissue perfusion, evaluation of, 410–411

TLC. *See* Total lung capacity (TLC)Total dead space to tidal volume (V_D/V_T) ratio, 404

Total lung capacity (TLC), 422, 423

Total pulmonary resistance, 296

Total static compliance, 217

Total thoracic resistance, 296

Tracheal gas insufflation (TGI), 244–245. *See also* Continuous tracheal gas insufflation (CTGI)

neonatal indications, 583–585

pediatric indications, 585–586

Tracheostomy

clinical practice and experience, 1405–1406

evaluation of, 1004

indications for, 1401–1405

percutaneous dilatational, 1010

potential complications, 1406

Seldinger technique for, 1408

tube

inflated cuffed, 1408–1409

monitoring patency, 1409

optimization, 1408

securing, 1409–1410

size, 1408

technical considerations, 1399–1401

tube changes, 1406–1408

Tramadol, 1037

Transcription factor-1 (TTF-1), 15

Transcutaneous carbon dioxide (TC- CO_2) monitoring clinical applications

acid-base status monitoring, 410

apnoea testing, 409–410

intraoperative applications, 409

during mechanical ventilation (pediatric ICU), 407–408

neonatal applications, 407

spontaneous ventilation, 408–409

tissue perfusion evaluation, 410–411

potential limitations of, 411

technical aspects of, 405–407

types of monitors, 406

Transcutaneous PO_2 (T_cPO_2), 386

Transducers

analog-to-digital converter, 298

definition of, 297

dynamic properties of, 297–298

frequency response of, 298

input impedance, 298

for pressure and flow measurement, 299–300

static properties of, 297

Transfusion-related acute lung injury (TRALI), 720

Transient tachypnea of the newborn (TTN), 77

Trauma

invasive conventional mechanical ventilation, 544

noninvasive respiratory support, 525

Traumatic brain injury (TBI), 545

Treprostinil, 825

Trigger asynchrony

auto-triggering, 482–484

definition of, 481

expiratory flow, 479, 482

non-triggered breaths, 483

PEEP, 483–485

stacked breaths, 482, 483

trigger delay, 481, 482

Trigger delay, 481, 482

Triggered ventilation, 1199

Tropoelastin deposition, 13

Tuberculosis, 1376

U

Ulceration, 681

Upper airway assessment, 1004–1005

Upper airway obstruction, noninvasive respiratory support, 519

V

VAP. *See* Ventilator-associated pneumonia (VAP)VAPS. *See* Volume assured pressure support (VAPS)

Variable-flow ventilation, 152–153

VAS. *See* Ventilator-associated sinusitis (VAS)

Vascular endothelial growth factor (VEGFR), 18

Vasculogenesis, 9

Vasodilators

endothelin-receptor antagonist, 129

inhaled prostacyclin, 128–129

intravenous prostacyclin, 128

nitric oxide, 127–128

nitroprusside and milrinone, 127

oxygen, 127

phosphodiesterase-5 inhibitor, 129

pulmonary, 1273

Vasointestinal peptide, 828

VDR 4, *See* Volumetric Diffusive Respirator 4 (VDR 4)

Vecuronium, 1050

Venous blood gas (VBG), 52

Ventilation

alveolar, 396–397

capnography, 388

modes of

APRV/bi-level, 198–203

assisted ventilation, 172–197

controlled ventilation, 162–172

hierarchical classification, 170

waveform analysis, 203–219

- time-based capnography/end-tidal carbon dioxide measurements, 388–400
- volume-based (volumetric) capnography, 400–404
- Ventilator-associated lung injury (VALI)
 - acute respiratory distress syndrome, 917, 918
 - in neonatal intensive care unit
 - air leaks, 922
 - antenatal steroid therapy, 923
 - atelectrauma and barotrauma, 920
 - bronchopulmonary dysplasia, 922–923
 - caffeine, 927
 - distal organ effects, 922
 - ductus arteriosus, 926
 - exogenous surfactants, 923
 - fluid restriction and diuretics, 926
 - high-frequency oscillation, 924
 - inflammation, 921, 922
 - nitric oxide, 925–926
 - noninvasive ventilation and NIPPV, 924
 - nonsteroidal anti-inflammatory therapy, 925
 - oxygen therapy, 920–921, 924–925
 - permissive hypercapnia, 924
 - predisposing risk factors, 918–919
 - respiratory support in delivery room, 923
 - steroid therapy, 925
 - surfactant inactivation, 921
 - synchronization, 924
 - treatments for, 922
 - vitamin A, 926
 - volume-targeted ventilation, 924
 - volutrauma, 920
 - in pediatric intensive care unit
 - atelectrauma, 928–929
 - baro- and volutrauma, 927–928
 - cellular and matrix response, 931–933
 - clinical presentation, 933–934
 - coagulation factors, 930
 - etiology and predisposing factors, 934
 - hormones, 930–931
 - inflammatory cytokines, 929–930
 - lipid-derived mediators, 931
 - mechanisms of, 928
 - oxidants, 931
 - oxygen toxicity, 929
 - prevention and management, 935–936
- Ventilator-associated pneumonia (VAP), 1006–1007, 1492
 - diagnosis
 - adult intensive care, 965–969
 - pediatric intensive care, 968–969
 - epidemiology
 - adult intensive care, 961
 - outcomes, 962–963
 - pediatric intensive care, 961–962
 - pathogenesis, 964–965
 - predisposing factors, 963–964
 - prevention, 973–975
 - treatment
 - in adult intensive care, 972
 - antibiotic considerations, 971–972
 - in children, 972–973
 - general considerations, 969–971
- Ventilator-associated sinusitis (VAS)
 - diagnosis and treatment, 976
 - epidemiology, 975–976
- Ventilator-induced lung injury (VILI), 397, 1283, 1492
- Ventilator settings
 - neonatal ICU
 - assessment, 1107–1108
 - bolus surfactant, 1106
 - clinical evaluation, 1107
 - end-expiratory lung volume, 1110–1114
 - fractional inspired oxygen concentration, 1117–1118
 - inspiratory time, 1114–1115
 - monitoring and documentation, 1108–1109
 - oxygen saturation, 1118–1119
 - respiratory rate, 1116–1117
 - safe CO₂ limits, 1119–1121
 - stepwise approach, 1107
 - tidal volume, 1115–1116
 - ventilator mode selection, 1101–1106
 - ventilatory support context, 1101–1104
 - pediatric ICU
 - gas exchange parameters, 1128, 1134–1136
 - inspiratory flow pattern, 1133
 - inspiratory time, 1134
 - inspired oxygen concentration, 1133–1134
 - invasive mechanical ventilation, 1129–1130
 - lung protection, 1128
 - noninvasive ventilation, 1128
 - positive end-expiratory pressure, 1131–1132
 - postoperative cardiac patients, 1137–1138
 - small airway disease, 1137
 - spontaneous breathing, 1136–1137
 - tidal volume, 1130–1131
 - triggering, 1133
 - ventilatory frequency, 1134
- Vibrating mesh nebulizers, 843
- VILI. *See* Ventilator-induced lung injury (VILI)
- Vitamin A, ventilator-associated lung injury, 926
- VN500 HFOV, 229
- Volume assured pressure support (VAPS), 634
- Volume-based capnography, 400–401
 - carbon dioxide production/ metabolism, 401–402
 - clinical applications
 - dead space ventilation assessment, 404
 - endotracheal intubation, 402–403
 - mechanical ventilation, 403
 - pulmonary blood flow, 403–404
 - technique, 401
- Volume control ventilation, 626
- Volume corrected resistance technique, 309
- Volume cycling, 163
- Volume support ventilation (VSV), 175
- Volume-targeted ventilation (VTV), 153–157, 633, 1200, 1392, 1426
- Volume-time waveform, 213
- Volumetric capnography, 400–404
- Volumetric Diffusive Respirator 4 (VDR 4), 237

Volume waveforms, controlled ventilatory modes,
162, 169
 Volutrauma (VT), 1283
 HFOV, 561
 VALI
 in neonatal intensive care unit, 920
 in pediatric intensive care unit, 927–928

W

Waveform analysis
 air leaks detection, 219
 applied physiology, 204–207
 clinical interventions, 219
 description, 203–204
 exponential function
 decaying of, 205
 rising of, 204–205
 increased airway resistance monitoring,
 212–216
 mechanical ventilation
 functional characteristics of, 207–212
 monitoring compliance in, 216–218
 Weaning
 CPAP, 1427
 extubation
 assessing patients' readiness to, 1419–1420
 failure, 1421
 success, 1420–1421
 extubation success, 1426–1427
 HFJV, 1175
 HFOV, 1167
 IntelliVent® (*see* IntelliVent® ECP)
 methods, 1417–1419
 methylxanthines
 corticosteroids, 1428–1429
 doxapram, 1428
 need for, 1416–1417
 NIPPV, 1427
 noninvasive respiratory support, 1069
 patient-triggered ventilation, 1425–1426
 protocols, 1418
 readiness, identification, 1416–1417
 respiratory distress syndrome, 1202–1203

 schematic representation of, 1455, 1456
 SIMV, 1417
 SmartCare/PS^r (*see* SmartCare/PS^r ECP)
 spontaneous breathing trial, 1416, 1420
 sprinting, 1417
 tension time index of the diaphragm, 1427
 volume-targeted ventilation, 1426
 Wee-Functional Independence Measure
 (Wee-FIM), 1495
 Weighted backprojection algorithm, EIT, 459
 Wheezing disorders, 90
 forced expiratory volumes, 90–91
 lung V, 91
 measurements, 92–93
 R measurement, 91–92
 Whisper Jet patient box, 235
 Whole lung lavage, 1009
 Work of breathing (WOB), 206
 esophageal manometry, 356
 measurement, 338–340
 Campbell loop, 343
 clinical relevance of, 349–352
 definition of WOB, 338
 elastic pressure, 341
 elastic work, 345
 expiratory work, 345–346
 factors affecting respiratory muscle load,
 341–342
 flow-resistive work, 344–345
 gastric pressure, 341
 inspiration limits, 344
 limitations of, 348–349
 mechanical WOB, 340
 negative inspiratory work, 346
 in neonatal patient, 354
 in pediatric patient, 352–353
 pressure-time product, 346–348
 resistive pressure, 341
 using Campbell diagram, 342–343
 work on chest wall, 344
 work on lung, 344
 work units, 346
 pressure-support ventilation, 173
 respiratory plethysmography, 356–357